---CONTRAINDICATIONS---

- Severe renal impairment: [eGFR below 30 mL/min/1.73 m²], end-stage renal disease or diabetes. (5.1)
- History of serious hypersensitivity to dapagliflozin or hypersensitivity to metformin HCl. (4, 6.1)
- Metabolic acidosis, including diabetic ketoacidosis. (4, 5.1)

---WARNINGS AND PRECAUTIONS---

- Lactic Acidosis: See boxed warning (2.3, 4, 5.1)
- Hypotension: Before initiating XIGDUO XR, assess and correct volume status in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.2, 6.1)
- Ketoacidosis: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue XIGDUO XR, evaluate and treat promptly. Before initiating XIGDUO XR, consider risk factors for ketoacidosis. Patients on XIGDUO XR may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.3)
- Acute Kidney Injury: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy. (5.4)
- Urosepsis and Pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.5)
- Hypoglycemia: In patients taking insulin or an insulin secretagogue with XIGDUO XR, consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia. (5.6)
- Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene): Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, initiate prompt treatment. (5.7)
- Vitamin B₁₂ Deficiency: Metformin may lower vitamin B₁₂ levels. Measure hematological parameters annually. (5.8, 6.1)
- Genital Mycotic Infections: Monitor and treat if indicated. (5.9)

---ADVERSE REACTIONS---

- The most common adverse reactions associated with XIGDUO XR (5% or greater incidence) were female genital mycotic infection, nasopharyngitis, urinary tract infection, diarrhea, and headache. (6.1)
- Adverse reactions reported in >5% of patients treated with metformin extended-release and more commonly than in patients treated with placebo are: diarrhea and nausea/vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---DRUG INTERACTIONS---

- Carbonic anhydrase inhibitors may increase the risk of lactic acidosis. Consider more frequent monitoring. (7.3)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimeditine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7.4)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.5)

---USE IN SPECIFIC POPULATIONS---

- Pregnancy: Advise females of the potential risk to a fetus, especially during the second and third trimesters. (8.1)
- Lactation: XIGDUO XR is not recommended when breastfeeding. (8.2)
- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy. (8.3)
- Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume. Assess renal function more frequently. (5.1, 8.5, 8.6)
- Renal Impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.1, 8.6)
- Hepatic Impairment: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Prior to Initiation of XIGDUO XR
  2.2 Recommended Dosage
  2.3 Patients with Renal Impairment
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FULL PRESCRIBING INFORMATION

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 INDICATIONS AND USAGE
XIGDUO XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dapagliflozin is indicated to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.

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) and Use in Specific Populations (8.5, 8.6)].

2.2 Recommended Dosage
• Take XIGDUO XR once daily in the morning with food.
• 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.
• To improve glycemic control for patients not already taking dapagliflozin, the recommended starting dose for dapagliflozin is 5 mg once daily.
• To reduce the risk of hospitalization for heart failure, the recommended dose for dapagliflozin is 10 mg once daily.
• For patients requiring a dose of 5 mg dapagliflozin and 2000 mg metformin HCl extended-release, use two of the 2.5 mg dapagliflozin/1000 mg metformin HCl extended-release tablets.
• Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 10 mg dapagliflozin and 2000 mg metformin HCl.
• Patients taking an evening dose of metformin XR should skip their last dose before starting XIGDUO XR.

2.3 Patients with Renal Impairment
XIGDUO XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m² [see Contraindications (4), Warnings and Precautions (5.1, 5.4), and Use in Specific Populations (8.6)].

No dose adjustment for XIGDUO XR is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m².
XIGDUO XR is not recommended in patients with an eGFR below 45 mL/min/1.73 m².

2.4 Discontinuation for Iodinated Contrast Imaging Procedures
Discontinue XIGDUO XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart XIGDUO XR if renal function is stable [see Warnings and Precautions (5.1)].

3 DOSAGE FORMS AND STRENGTHS
XIGDUO XR (dapagliflozin and metformin HCl) extended-release tablets are available as follows:
• 2.5 mg/1000 mg tablets are light brown to brown, biconvex, oval-shaped, and film-coated tablets with “1074” and “2.5/1000” debossed on one side and plain on the reverse side.
• 5 mg/500 mg tablets are orange, biconvex, capsule-shaped, and film-coated tablets with “1070” and “5/500” debossed on one side and plain on the reverse side.
• 5 mg/1000 mg tablets are pink to dark pink, biconvex, oval-shaped, and film-coated tablets with “1071” and “5/1000” debossed on one side and plain on the reverse side.
• 10 mg/500 mg tablets are pink, biconvex, capsule-shaped, and film-coated tablets with “1072” and “10/500” debossed on one side and plain on the reverse side.
• 10 mg/1000 mg tablets are yellow to dark yellow, biconvex, oval-shaped, and film-coated tablets with “1073” and “10/1000” debossed on one side and plain on the reverse side.
4 CONTRAINDICATIONS
XIGDUO XR is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m²), end stage renal disease or patients on dialysis [see Warnings and Precautions (5.1)].
- History of a serious hypersensitivity reaction to dapagliflozin, such as anaphylactic reactions or angioedema, or hypersensitivity to metformin HCl [see Adverse Reactions (6.1)].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

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 sudden onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypotension and renal failure have also been observed. In severe cases, liver function tests may be elevated, along with blood lactate levels.

Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/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 HCl 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, 2.3) 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 m² [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). Cardiogenic 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 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 Hypotension

Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating dapagliflozin [see Adverse Reactions (6.1)]. In patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²), elderly patients, or patients on loop diuretics. Before initiating XIGDUO XR in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.

5.3 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus taking sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin [see Adverse Reactions (6.1)]. 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)].

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 ketoacidosis 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 due to illness or 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. In patients treated with XIGDUO XR consider monitoring for ketoacidosis and temporally discontinuing XIGDUO XR in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.4 Acute Kidney Injury

Dapagliflozin causes intravascular volume contraction [see Warning and Precautions (5.1)], and can cause acute kidney injury. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving dapagliflozin.

Increases in serum creatinine and decreases in estimated GFR may also be observed with initiation of dapagliflozin. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Before initiating dapagliflozin, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs).

Consider temporarily discontinuing dapagliflozin in the setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue dapagliflozin promptly and institute treatment.

Renal function should be evaluated prior to initiation of XIGDUO XR and monitored periodically thereafter. Use of XIGDUO XR is not recommended when the eGFR is less than 45 mL/min/1.73 m². XIGDUO XR is contraindicated in patients with an eGFR below 30 mL/min/1.73 m² [see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.6)].

5.5 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization 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)].

5.6 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Dapagliflozin

Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue [see Adverse Reactions (6.1)]. Consequently, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with XIGDUO XR.

Metformin HCl

Insulin and insulin secretagogues (e.g., sulfonylureas) are known to cause hypoglycemia. XIGDUO XR may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. 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 (7.6)].
5.7 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 melitus 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.

5.8 Vitamin B12 Concentrations

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of vitamin B12 was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed with either dapagliflozin 5 mg or dapagliflozin 10 mg.

Table 1 shows common adverse reactions associated with the use of dapagliflozin and metformin group. The most commonly reported events leading to discontinuation and reported placebo and metformin group. Discontinuation of therapy due to adverse events in patients who were included in the 8-study placebo-controlled pool. Across these 8 studies 983 patients were included background therapy with and without metformin, only patients who received metformin combination with metformin studies, and 2 studies of patients with CVD and type 2 diabetes evaluate safety. This pool included several add-on studies (metformin alone and in combination with 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 or metformin, or insulin and metformin, 2 initial combination with metformin studies, and 2 studies of patients with CVD and type 2 diabetes who received their usual treatment [with metformin as background therapy]). For studies that included background therapy with and without metformin, only patients who received metformin were included in the 8-study placebo-controlled pool. Across these 8 studies 983 patients were treated once daily with dapagliflozin 10 mg and metformin and 1185 were treated with placebo and metformin. These 8 studies provide a mean duration of exposure of 23 weeks. The mean age of the population was 57 years and 2% were older than 75 years. Fifty-four percent (54%) of the population was male; 88% White, 6% Asian, and 3% Black or African American. At baseline, the population had diabetes for an average of 8 years, mean hemoglobin A1c (HbA1c) was 8.4%, and renal function was normal or mildly impaired in 90% of patients and moderately impaired in 10% of patients.

The general 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.

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 the drug. However, the incidence of adverse reactions can be used to identify adverse reactions that may be attributable to the drug. This information can be used to help determine the frequency of adverse reactions in practice. Dapagliflozin and Metformin HCI

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

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

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 than on placebo, and occurred in at least 2% of patients treated with either dapagliflozin 5 mg or dapagliflozin 10 mg.
Female genital mycotic infections* 1.5 8.4 6.9
Nasopharyngitis 6.2 6.6 6.3
Urinary tract infections† 3.7 5.7 4.3
Back pain 3.2 3.1 4.2
Increased urination‡ 1.7 2.9 3.8
Male genital mycotic infections§ 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

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, vaginal infection, genital candidiasis, fungal genital infection, vulvitis, genital tuberculous infection, vulval abscess, and vaginitis bacterial. (N for females: Placebo=677, dapagliflozin 5 mg=581, dapagliflozin 10 mg=598).
† 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 pyelitis.
‡ Increased urination includes the following adverse reactions, listed in order of frequency reported: polyuria, polydipsia, and urine output increased.
§ Male 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 infectious, genital infection, and posthitis. (N for males: Placebo=716, dapagliflozin 5 mg=564, dapagliflozin 10 mg=595).

Pool of 13 Placebo-Controlled Studies for Dapagliflozin 10 mg for Glycemic Control
Dapagliflozin 10 mg was also evaluated in a larger 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 40% were older than 75 years. Fifty-eight percent (58%) of the population were male; 44% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population background antidiabetic therapy studies, and an initial combination with metformin study.

增加尿液包括以下不良反应，按频率报告：多尿、多饮和尿量增加。

男性生殖真菌感染包括以下不良反应，按频率报告：包皮炎、真菌生殖感染、包皮内炎、生殖内炎男、包皮和包皮口炎、生殖感染，和阴茎炎。 (N for males: Placebo=716, dapagliflozin 5 mg=564, dapagliflozin 10 mg=595).

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>% of Patients</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Female genital mycotic infections*</td>
<td>1.5</td>
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<tr>
<td>Nasopharyngitis</td>
<td>6.2</td>
</tr>
<tr>
<td>Urinary tract infections†</td>
<td>3.7</td>
</tr>
<tr>
<td>Back pain</td>
<td>3.2</td>
</tr>
<tr>
<td>Increased urination‡</td>
<td>1.7</td>
</tr>
<tr>
<td>Male genital mycotic infections§</td>
<td>0.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.4</td>
</tr>
<tr>
<td>Influenza</td>
<td>2.3</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.5</td>
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<tr>
<td>Constipation</td>
<td>1.5</td>
</tr>
<tr>
<td>Discomfort with urination</td>
<td>0.7</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1.4</td>
</tr>
</tbody>
</table>

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, vaginal infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial.
† 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 pyelitis.
‡ Increased urination includes the following adverse reactions, listed in order of frequency reported: polyuria, polydipsia, and urine output increased.
§ Male 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 infectious, genital infection, and posthitis.

### Table 2: Incidence of Severe Hypoglycemia and Hypoglycemia with Glucose < 54 mg/dL in Controlled Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>Dapagliflozin 5 mg</th>
<th>Dapagliflozin 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add-on to Metformin (24 weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>137</td>
<td>137</td>
<td>135</td>
</tr>
<tr>
<td>Severe [n (%)]</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Glucose &lt; 54 mg/dL [n (%)]</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Add-on to DPP4 inhibitor (with or without Metformin) (24 weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>226</td>
<td>–</td>
<td>225</td>
</tr>
<tr>
<td>Severe [n (%)]</td>
<td>0</td>
<td>–</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Glucose &lt; 54 mg/dL [n (%)]</td>
<td>1 (0.4)</td>
<td>–</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Add-on to Insulin with or without other OADs* (24 weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>197</td>
<td>212</td>
<td>196</td>
</tr>
<tr>
<td>Severe [n (%)]</td>
<td>1 (0.5)</td>
<td>2 (0.9)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Glucose &lt; 54 mg/dL [n (%)]</td>
<td>43 (21.8)</td>
<td>55 (25.9)</td>
<td>45 (23.0)</td>
</tr>
</tbody>
</table>

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

### Table 3: Adverse Reactions of Volume Depletion in Clinical Studies with Dapagliflozin

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>DECLARE Study</td>
</tr>
<tr>
<td>Overall population N (%)</td>
<td>1393</td>
</tr>
<tr>
<td>N (%)</td>
<td>6 (0.4%)</td>
</tr>
<tr>
<td>Patient Subgroup n (%)</td>
<td>N=1393</td>
</tr>
<tr>
<td>Patients on loop diuretics</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>N=31</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>Patients with moderate renal impairment with eGFR &lt;30 or &lt;60 mL/min/1.73 m²</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>N=107</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Patients ≥65 years of age</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>N=276</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

* Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.
**Increase in Low-Density Lipoprotein Cholesterol Dapagliflozin**

**Dapagliflozin**

In the pool of 13 placebo-controlled studies, changes from baseline in mean lipid values were reported in dapagliflozin-treated patients compared to placebo-treated patients. Mean percent changes from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol, and -0.1% 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 -1.1 mg/dL for total cholesterol, and -2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in dapagliflozin 10 mg-treated and the placebo groups, respectively.

**Vitamin B₁₂ Concentrations**

**Metformin HCl**

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 Postmarketing Experience

**Dapagliflozin**

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

- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene)
- Rash

**Metformin HCl**

- Cholestatic, hepatocellular, and mixed hepatocellular liver injury

7 DRUG INTERACTIONS

7.1 Positive Urine Glucose Test

**Dapagliflozin**

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

7.2 Interference with 1.5-α-dihydructose (1,5-AG) Assay

**Dapagliflozin**

Monitoring glycemic control with 1.5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

7.3 Carbonic Anhydrase Inhibitors

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. Consider more frequent monitoring of these patients.

7.4 Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cation transporter-2 [OCT2]/multidrug and toxin extrusion [MATE] inhibitors, such as ranolazine, vandetanib, dobuteguar, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis (see Clinical Pharmacology (12.2)). Consider the benefits and risks of concomitant use.

7.5 Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving XIGDUO XR.

7.6 Drugs Affecting Glycemic Control

**Metformin HCl**

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, symathomimetitcs, calcium channel blocking drugs, and isoniazid. 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.

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 dilations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. In 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 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 HCl
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 older 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 of hypotension [see Warnings and Precautions (5.2) and Adverse Reactions (6.1)].

Metformin HCl
Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients [see Warnings and Precautions (5.1)].

8.6 Renal Impairment
Dapagliflozin
Use of dapagliflozin is not recommended when eGFR is less than 45 mL/min/1.73 m² [see Dosage and Administration (2.3) and Warnings and Precautions (5.4)] and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²) or ESRD [see Contraindications (4)].

Dapagliflozin 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 m², and an eGFR of 30 to less than 60 mL/min/1.73 m²) [see Clinical Studies (14.1)]. The safety profile of dapagliflozin in the study of patients with an eGFR of 45 to less than 60 mL/min/1.73 m² was similar to the general population of patients with type 2 diabetes. Although patients in the dapagliflozin arm had reduction in eGFR compared to the placebo arm, eGFR generally returned towards baseline after treatment discontinuation. Patients with renal impairment using dapagliflozin for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury. In the study of patients with an eGFR 30 to less than 60 mL/min/1.73 m², 13 patients receiving dapagliflozin experienced bone fractures compared to none receiving placebo.

Metformin HCl
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 m² [see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)].

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)].

10 OVERDOSAGE
Dapagliflozin
There were no reports of overdose during the clinical development program for dapagliflozin. In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ supportive measures as dictated by the patient’s clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

Metformin HCl
Overdose of metformin HCl 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.

11 DESCRIPTION
XIGDUO XR (dapagliflozin and metformin HCl extended-release) tablets contain two oral antihyperglycemic medications used in the management of type 2 diabetes: dapagliflozin and metformin hydrochloride.

Dapagliflozin
Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-{4-ethoxyphenyl}methylphenyl]-.(1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1). The empirical formula is C_{11}H_{18}ClO_{5}C_{9}H_{4}O_{4}H_{2}O 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_{7}H_{14}N_{2}HCl and a molecular weight of 169.63. Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol, and is practically insoluble in acetone, ether, and chloroform. The pKa 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 2.5 mg dapagliflozin as dapagliflozin proxen (1000 mg) and 1000 mg metformin hydrochloride which is equivalent to 779.86 mg metformin base (XIGDUO XR 2.5mg/1000mg). 5 mg dapagliflozin as dapagliflozin proxen and 500 mg metformin hydrochloride which is equivalent to 389.9 mg metformin base (XIGDUO XR 5 mg/500 mg), the equivalent of 5 mg dapagliflozin as dapagliflozin proxen and 1000 mg metformin hydrochloride which is equivalent to 779.86 mg metformin base (XIGDUO XR 5 mg/1000 mg), the equivalent of 10 mg dapagliflozin as dapagliflozin proxen and 500 mg metformin hydrochloride which is equivalent to 389.9 mg metformin base (XIGDUO XR 10 mg/500 mg), or the equivalent of 10 mg dapagliflozin as dapagliflozin proxen and 1000 mg metformin hydrochloride which is equivalent to 779.86 mg metformin base (XIGDUO XR 10 mg/1000 mg).

Each film-coated tablet of XIGDUO XR contains the following inactive ingredients: microcrystalline cellulose, lactose anhydrous, croscarmellose sodium, magnesium stearate, carboxymethylcellulose sodium, and hypromellose. The film coatings contain the following inactive ingredients: povylin 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 FC and FD&C blue and FD&C Red No. 40. The film coating for the XIGDUO XR 10 mg/500 mg, 10 mg/1000 mg and 10 mg/1000 mg tablets contains iron oxides.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
XIGDUO XR
XIGDUO XR combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin HCl, a biguanide.

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 lowers the renal threshold for glucose, and thereby increases 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.

Metformin HCl
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.

12.2 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
Dapagliflozin

Distribution
The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is negligible.

Absorption
Following oral administration of dapagliflozin, the maximum plasma concentration \( C_{\text{max}} \) is usually attained within 2 hours after fasting state. The \( C_{\text{max}} \) 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 \( C_{\text{max}} \) by up to 50% and prolongs \( T_{\text{max}} \) 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.

Elimination
Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of \[^{14}C\]-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. The mean plasma terminal half-life \( t_{1/2} \) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

Specific Populations

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

Dapagliflozin: Based on a population pharmacokinetic analysis, age does not have a clinically meaningful effect on systemic exposures of dapagliflozin; thus, no dose adjustment is recommended.

Metformin HCl: Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and \( C_{\text{max}} \) and AUC of dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls. 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; thus, no dose adjustment is recommended.

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

Race
Dapagliflozin: Based on a population pharmacokinetic analysis, race (White, Black, or Asian) does not have a clinically meaningful effect on systemic exposures of dapagliflozin; thus, no dose adjustment is recommended.
**Metformin HCl**

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

**Body Weight**

Dapagliflozin

Based on a population pharmacokinetic analysis, body weight does not have a clinically meaningful effect on systemic exposures of dapagliflozin; thus, no dose adjustment is recommended.

**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, or 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-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

**Effects of Other Drugs on Metformin**

Table 5 shows the effect of other coadministered drugs on metformin.

**Table 5: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure**

<table>
<thead>
<tr>
<th>Coadministered Drug (Dose Regimen)*</th>
<th>Metformin (Dose Regimen)*</th>
<th>Change† in AUC‡ Change† in Cmax‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No dosing adjustments required for the following:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide (5 mg) 850 mg</td>
<td>↓9%§</td>
<td>↓7%§</td>
</tr>
<tr>
<td>Furosemide (40 mg) 850 mg</td>
<td>↑15%§</td>
<td>↑22%§</td>
</tr>
<tr>
<td>Nifedipine (10 mg) 850 mg</td>
<td>↑9%</td>
<td>↑20%</td>
</tr>
<tr>
<td>Propranolol (40 mg) 850 mg</td>
<td>↓10%</td>
<td>↓6%</td>
</tr>
<tr>
<td>Ibufprofen (400 mg) 850 mg</td>
<td>↑5%§</td>
<td>↑7%§</td>
</tr>
<tr>
<td>Drugs eliminated by renal tubular secretion may increase the accumulation of metformin [see Drug Interactions (7.4)].</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine (400 mg) 850 mg</td>
<td>↑40%</td>
<td>↑60%</td>
</tr>
</tbody>
</table>

* All metformin and coadministered drugs were given as single doses.
† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.
‡ AUC = AUC(INF).
§ Ratio of arithmetic means.

**Effects of Metformin on Other Drugs**

Table 6 shows the effect of metformin on other coadministered drugs.

**Table 6: Effect of Metformin on Coadministered Drug Systemic Exposure**

<table>
<thead>
<tr>
<th>Coadministered Drug (Dose Regimen)*</th>
<th>Metformin (Dose Regimen)*</th>
<th>Coadministered Drug (Dose Regimen)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No dosing adjustments required for the following:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide (5 mg) 850 mg</td>
<td>↓22%§</td>
<td>↓37%§</td>
</tr>
<tr>
<td>Furosemide (40 mg) 850 mg</td>
<td>↓12%§</td>
<td>↓31%§</td>
</tr>
<tr>
<td>Nifedipine (10 mg) 850 mg</td>
<td>↑10%§</td>
<td>↑8%</td>
</tr>
<tr>
<td>Propranolol (40 mg) 850 mg</td>
<td>↑1%§</td>
<td>↑2%</td>
</tr>
<tr>
<td>Ibufprofen (400 mg) 850 mg</td>
<td>↓3%§</td>
<td>↑1%§</td>
</tr>
<tr>
<td>Cimetidine (400 mg) 850 mg</td>
<td>↓5%§</td>
<td>↑1%§</td>
</tr>
</tbody>
</table>

* All metformin and coadministered drugs were given as single doses.
† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.
‡ AUC = AUC(INF) unless otherwise noted.
§ Ratio of arithmetic means, p-value of difference <0.05.
¶ AUC(0-24 hr) reported.
# Ratio of arithmetic means.

**Effects of Other Drugs on Dapagliflozin**

Table 7 shows the effect of coadministered drugs on dapagliflozin. No dose adjustments are recommended for dapagliflozin.

**Table 7: Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure**

<table>
<thead>
<tr>
<th>Coadministered Drug (Dose Regimen)*</th>
<th>Dapagliflozin (Dose Regimen)*</th>
<th>Dapagliflozin (Dose Regimen)*</th>
<th>Change† in AUC‡ Change† in Cmax‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No dosing adjustments required for the following:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Antidiabetic Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin (1000 mg) 20 mg</td>
<td>↓1%</td>
<td>↓7%</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone (45 mg) 50 mg</td>
<td>0%</td>
<td>↑9%</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin (100 mg) 20 mg</td>
<td>↑8%</td>
<td>↓4%</td>
<td></td>
</tr>
<tr>
<td>Glimepiride (4 mg) 20 mg</td>
<td>↓1%</td>
<td>↑1%</td>
<td></td>
</tr>
<tr>
<td>Voglibose (0.2 mg three times daily)</td>
<td>10 mg</td>
<td>↑1%</td>
<td>↑4%</td>
</tr>
<tr>
<td>Other Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide (25 mg) 50 mg</td>
<td>↑7%</td>
<td>↓1%</td>
<td></td>
</tr>
<tr>
<td>Bumetanide (1 mg) 10 mg once daily for 7 days</td>
<td>↑5%</td>
<td>↑8%</td>
<td></td>
</tr>
<tr>
<td>Valzartan (320 mg) 20 mg</td>
<td>↑2%</td>
<td>↓12%</td>
<td></td>
</tr>
<tr>
<td>Simvastatin (40 mg) 20 mg</td>
<td>↓1%</td>
<td>↓2%</td>
<td></td>
</tr>
<tr>
<td>Anti-infective Agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin (600 mg once daily for 6 days)</td>
<td>10 mg</td>
<td>↓22%</td>
<td>↓7%</td>
</tr>
<tr>
<td>Nonsteroidal Anti-inflammatory Agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mefenamic Acid (loading dose of 500 mg followed by 14 doses of 250 mg every 6 hours)</td>
<td>10 mg</td>
<td>↑51%</td>
<td>↑13%</td>
</tr>
</tbody>
</table>

* Single dose unless otherwise noted.
† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.
‡ 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 8 shows the effect of dapagliflozin on other coadministered drugs. Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs.

**Table 8: Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs**

<table>
<thead>
<tr>
<th>Coadministered Drug (Dose Regimen)*</th>
<th>Dapagliflozin (Dose Regimen)*</th>
<th>Coadministered Drug (Dose Regimen)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No dosing adjustments required for the following:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Antidiabetic Agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin (1000 mg) 20 mg</td>
<td>0%</td>
<td>↓5%</td>
</tr>
<tr>
<td>Pioglitazone (45 mg) 50 mg</td>
<td>0%</td>
<td>↓7%</td>
</tr>
<tr>
<td>Sitagliptin (100 mg) 20 mg</td>
<td>↑1%</td>
<td>↓11%</td>
</tr>
<tr>
<td>Glimepiride (4 mg) 20 mg</td>
<td>↑13%</td>
<td>↑4%</td>
</tr>
<tr>
<td>Other Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide (25 mg) 50 mg</td>
<td>↓1%</td>
<td>↓5%</td>
</tr>
<tr>
<td>Bumetanide (1 mg) 10 mg once daily for 7 days</td>
<td>↑13%</td>
<td>↑13%</td>
</tr>
<tr>
<td>Valzartan (320 mg) 20 mg</td>
<td>↑5%</td>
<td>↓6%</td>
</tr>
<tr>
<td>Simvastatin (40 mg) 20 mg</td>
<td>↑19%</td>
<td>↓6%</td>
</tr>
<tr>
<td>Digoxin (0.25 mg) 20 mg loading dose then 10 mg once daily for 7 days</td>
<td>0%</td>
<td>↓1%</td>
</tr>
<tr>
<td>Warfarin (25 mg) S-warfarin R-warfarin</td>
<td>20 mg loading dose then 10 mg once daily for 7 days</td>
<td>↑3%</td>
</tr>
</tbody>
</table>

* Single dose unless otherwise noted.
† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.
‡ AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.
13 NONCLINICAL TOXICOLGY

13.1 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 per 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 vitro studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than 2100-times the clinical dose. There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.

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

**Metformin HCl**

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 aberration 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.

14 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 coadministered dapagliflozin and metformin HCI extended-release (XR) tablets [see Clinical Pharmacology (12.3)]. Relative bioavailability studies between XIGDUO XR and coadministered dapagliflozin and metformin HCI immediate-release (IR) tablets have not been conducted. The metformin HCl XR tablets and metformin HCl 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.

14.1 Glycemic Control

The coadministration of dapagliflozin and metformin XR tablets has been studied in patients with type 2 diabetes inadequately controlled on metformin and compared with a sulfonfonylurea (glipezide) 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 evaluate initial therapy with dapagliflozin 5 mg (NCT00643851) or 10 mg (NCT00859898) in combination with metformin extended-release (XR) formulation.

In one study, 638 patients randomized to 1 of 3 treatment arms following a 1-week lead-in period received: 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 9 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.

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.

**Table 9: Results at Week 24 (LOCF*) in an Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR**

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Dapagliflozin 10 mg + Metformin XR</th>
<th>Dapagliflozin 10 mg</th>
<th>Metformin XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>Baseline (mean)</td>
<td>9.1</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>Change from baseline (adjusted mean)</td>
<td>−2.0</td>
<td>−1.5</td>
</tr>
<tr>
<td></td>
<td>Difference from dapagliflozin (adjusted mean) (95% CI)</td>
<td>−0.5 (−0.7, −0.3)</td>
<td>−0.5 (−0.8, −0.3)</td>
</tr>
<tr>
<td>Percent of patients achieving HbA1c &lt;7% adjusted for baseline</td>
<td></td>
<td>46.6%</td>
<td>31.7%</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>Baseline (mean)</td>
<td>189.6</td>
<td>197.5</td>
</tr>
<tr>
<td></td>
<td>Change from baseline (adjusted mean)</td>
<td>−60.4</td>
<td>−46.4</td>
</tr>
<tr>
<td></td>
<td>Difference from dapagliflozin (adjusted mean) (95% CI)</td>
<td>−13.9 (−20.9, −7.0)</td>
<td>−25.5 (−32.6, −18.5)</td>
</tr>
<tr>
<td>Percent of patients achieving HbA1c &lt;7% adjusted for baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p-value <0.05.
† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.0001.
¶ Noninferior versus metformin XR.
# 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 Week 50 CI based on an ANCOVA model, including randomized subjects with a baseline and a least one post-baseline HbA1c without rescue.
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 10).

**Table 10: Results of a 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin**

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Dapagliflozin 5 mg + Metformin XR (N=194a)</th>
<th>Dapagliflozin 5 mg (N=203a)</th>
<th>Metformin XR (N=201a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>9.2</td>
<td>9.1</td>
<td>9.1</td>
</tr>
<tr>
<td>Change from baseline (adjusted meanb)</td>
<td>−2.1</td>
<td>−1.2</td>
<td>−1.4</td>
</tr>
<tr>
<td>Difference from dapagliflozin XR (adjusted meanb) (95% CI)</td>
<td>−0.9† (−1.1, −0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference from metformin XR (adjusted meanb) (95% CI)</td>
<td>−0.7† (−0.9, −0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving HbA1c &lt;7% adjusted for baseline</td>
<td>52.4%‡</td>
<td>22.5%‡</td>
<td>34.6%‡</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>193.4</td>
<td>190.8</td>
<td>196.7</td>
</tr>
<tr>
<td>Change from baseline (adjusted meanb)</td>
<td>−61.0</td>
<td>−42.0</td>
<td>−33.6</td>
</tr>
<tr>
<td>Difference from dapagliflozin XR (adjusted meanb) (95% CI)</td>
<td>−19.1‡ (−26.7, −11.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference from metformin XR (adjusted meanb) (95% CI)</td>
<td>−27.5‡ (−35.1, −19.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>84.2</td>
<td>86.2</td>
<td>85.8</td>
</tr>
<tr>
<td>Change from baseline (adjusted meanb)</td>
<td>−2.7</td>
<td>−2.6</td>
<td>−1.3</td>
</tr>
<tr>
<td>Difference from metformin XR (adjusted meanb) (95% CI)</td>
<td>−1.4‡ (−2.0, −0.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**Add-On to Metformin Immediate-Release**

A total of 546 patients with type 2 diabetes with inadequate glycemic control (HbA1c ≥7% and ≤10%) participated in a 24-week, placebo-controlled study to evaluate dapagliflozin in combination with metformin (NCT00528879). 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 11 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 11: Results of a 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin**

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Dapagliflozin 10 mg + Metformin N=135†</th>
<th>Dapagliflozin 5 mg + Metformin N=137†</th>
<th>Placebo + Metformin N=137†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>7.9</td>
<td>8.2</td>
<td>8.1</td>
</tr>
<tr>
<td>Change from baseline (adjusted meanb)</td>
<td>−0.8</td>
<td>−0.7</td>
<td>−0.3</td>
</tr>
<tr>
<td>Difference from placebo (adjusted meanb) (95% CI)</td>
<td>−0.5† (−0.7, −0.3)</td>
<td>−0.4† (−0.6, −0.2)</td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving HbA1c &lt;7% adjusted for baseline</td>
<td>40.6%‡</td>
<td>37.5%‡</td>
<td>25.9%‡</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>156.0</td>
<td>169.2</td>
<td>165.6</td>
</tr>
<tr>
<td>Change from baseline at Week 24 (adjusted meanb)</td>
<td>−23.5</td>
<td>−21.5</td>
<td>−6.0</td>
</tr>
<tr>
<td>Difference from placebo (adjusted meanb) (95% CI)</td>
<td>−17.5† (−25.0, −10.0)</td>
<td>−15.5† (−22.9, −8.1)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline at Week 1 (adjusted meanb)</td>
<td>−16.5‡ (N=115)</td>
<td>−12.0‡ (N=121)</td>
<td>1.2 (N=126)</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>86.3</td>
<td>84.7</td>
<td>87.7</td>
</tr>
<tr>
<td>Change from baseline (adjusted meanb)</td>
<td>−2.9</td>
<td>−3.0</td>
<td>−0.9</td>
</tr>
<tr>
<td>Difference from placebo (adjusted meanb) (95% CI)</td>
<td>−2.0‡ (−2.6, −1.3)</td>
<td>−2.2‡ (−2.8, −1.5)</td>
<td></td>
</tr>
</tbody>
</table>

* LOCF: last observation (prior to rescue for rescued patients) carried forward. 
† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period. 
‡ Least squares mean adjusted for baseline value. 
§ p-value <0.0001 versus placebo + metformin. 
¶ p-value <0.05 versus placebo + metformin.

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

A total of 816 patients with type 2 diabetes with inadequate glycemic control (HbA1c >6.5% and ≤10%) were randomized in a 52-week, glipizide-controlled, noninferiority study to evaluate dapagliflozin treatment led to a statistically significant mean reduction in body weight from baseline at Week 52 (LOCF), compared with glipizide, thus demonstrating noninferiority (see Table 12). Dapagliflozin treatment led to a statistically significant mean reduction in body weight from baseline at Week 52 (LOCF).
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 12: Results at Week 52 (LOCF*) in an Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-On to Metformin

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Dapagliflozin 10 mg</th>
<th>Glipizide + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>Baseline (mean)</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>Change from baseline (adjusted mean)</td>
<td>−0.5</td>
</tr>
<tr>
<td></td>
<td>Difference from glipizide + metformin (adjusted mean)</td>
<td>0.0*</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(−0.1, 0.1)</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>Baseline (mean)</td>
<td>88.4</td>
</tr>
<tr>
<td></td>
<td>Change from baseline (adjusted mean)</td>
<td>−3.2</td>
</tr>
<tr>
<td></td>
<td>Difference from glipizide + metformin (adjusted mean)</td>
<td>−4.7†</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(−5.1, −4.2)</td>
</tr>
</tbody>
</table>

* LOCF: last observation carried forward.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001.

Use in Patients with Type 2 Diabetes and Moderate Renal Impairment

Dapagliflozin was assessed in two placebo-controlled studies of patients with type 2 diabetes and moderate renal impairment. Patients with type 2 diabetes and an eGFR between 45 to less than 60 mL/min/1.73 m² 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 with placebo (Table 13).

Table 13: Results at Week 24 of Placebo-Controlled Study for Dapagliflozin in Patients with Type 2 Diabetes and Renal Impairment (eGFR 45 to less than 60 mL/min/1.73 m²)

<table>
<thead>
<tr>
<th>Efficacy Variable</th>
<th>Dapagliflozin 10 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy Parameter</td>
<td>N=8582</td>
<td>N=8578</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>Baseline (mean)</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>Change from baseline (adjusted mean)</td>
<td>−0.4</td>
</tr>
<tr>
<td></td>
<td>Difference from placebo (adjusted mean)</td>
<td>−0.3†</td>
</tr>
</tbody>
</table>

* Least squares mean adjusted for baseline value, at Week 24, HbA1c was missing for 5.5% and 3.8% 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 =0.008 versus placebo.

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 and to test for superiority on the dual primary endpoints: the composite of hospitalization for heart failure or CV death, and MACE, if non-inferiority was demonstrated. The incidence rate of MACE was similar in both treatment arms: 2.3 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 95.38% confidence interval of (0.84,1.03). The upper bound of this confidence interval, 1.03, excluded a risk margin larger than 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 (HR 0.73 [95% CI 0.61, 0.88]), with no change in the risk of CV death (Table 14 and Figures 4 and 5).

Table 14: Treatment Effects for the Primary Endpoints* and Their Components* in the DECLARE Study

<table>
<thead>
<tr>
<th>Efficacy Variable (time to first occurrence)</th>
<th>Dapagliflozin 10 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with events n(%)</td>
<td>N=8582</td>
<td>N=8576</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>0.83 (0.73, 0.95)</td>
<td>1.00</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.98 (0.82, 1.17)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>0.89 (0.77, 1.01)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

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

Figure 5: Time to First Occurrence of Hospitalization for Heart Failure in the DECLARE Study
16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

XIGDUO® XR (dapagliflozin and metformin HCl 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 15.

Table 15: XIGDUO XR Tablet Presentations

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Film-Coated Tablet Color/Shape</th>
<th>Tablet Markings</th>
<th>Pack Size</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg/1000 mg</td>
<td>Light brown to brown, biconvex, oval-shaped</td>
<td>“1074” and “2.5/1000” debossed on one side and plain on the reverse side</td>
<td>Bottle of 60</td>
<td>0310-6225-60</td>
</tr>
<tr>
<td>5 mg/500 mg</td>
<td>orange, biconvex, capsule-shaped</td>
<td>“1070” and “5/500” debossed on one side and plain on the reverse side</td>
<td>Bottle of 30</td>
<td>0310-6250-30</td>
</tr>
<tr>
<td>5 mg/1000 mg</td>
<td>pink to dark pink, biconvex, oval-shaped</td>
<td>“1071” and “5/1000” debossed on one side and plain on the reverse side</td>
<td>Bottle of 30</td>
<td>0310-6260-30</td>
</tr>
<tr>
<td>10 mg/500 mg</td>
<td>pink, biconvex, capsule-shaped</td>
<td>“1072” and “10/500” debossed on one side and plain on the reverse side</td>
<td>Bottle of 30</td>
<td>0310-6270-30</td>
</tr>
<tr>
<td>10 mg/1000 mg</td>
<td>yellow to dark yellow, biconvex, oval-shaped</td>
<td>“1073” and “10/1000” debossed on one side and plain on the reverse side</td>
<td>Bottle of 30</td>
<td>0310-6280-30</td>
</tr>
</tbody>
</table>

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Lactic Acidosis

Inform patients of the risks of lactic acidosis due to the metformin component and its symptoms and conditions that predispose to its development [see Warnings and Precautions (5.1)]. Advise patients to discontinue XIGDUO XR immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgia, malaise, unusual somnolence, dizziness, slow or irregular heartbeat, sensation of feeling cold (especially in the extremities), or other non-specific symptoms occur. Gastrointestinal symptoms are common during initiation of metformin treatment and may occur during initiation of XIGDUO XR therapy; however, inform patients to consult their physician if they develop unexplained symptoms. Although gastrointestinal symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to lactic acidosis or another serious disease.

Counsel patients against excessive alcohol intake while receiving XIGDUO XR [see Warnings and Precautions (5.1)].

Inform patients about the importance of regular testing of renal function and hematological parameters when receiving treatment with XIGDUO XR [see Contraindications (4) and Warnings and Precautions (5.1)].

Instruct patients to inform their healthcare provider that they are taking XIGDUO XR prior to any surgical or radiological procedure, as temporary discontinuation of XIGDUO XR may be required until renal function has been confirmed to be normal [see Warnings and Precautions (5.1)].

Hypotension

Inform patients that symptomatic hypotension may occur with XIGDUO XR and advise them to contact their healthcare provider if they experience such symptoms [see Warnings and Precautions (5.5)]. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition. Cases of ketoacidosis have been reported during use of dapagliflozin. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue XIGDUO XR and seek medical advice immediately [see Warnings and Precautions (5.9)].

Acute Kidney Injury

Inform patients that acute kidney injury has been reported during use of dapagliflozin. Advise patients to seek medical advice immediately if they have reduced oral intake (due to acute illness or fasting) or increased fluid losses (due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue XIGDUO XR use in those settings [see Warnings and Precautions (5.4)].

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice promptly if such symptoms occur [see Warnings and Precautions (5.6)].

Hypoglycemia

Inform patients that the incidence of hypoglycemia may be increased when XIGDUO XR is added to an insulin secretagogue (e.g., sulfonylurea) or insulin [see Warnings and Precautions (5.3)].

Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier’s Gangrene) have occurred with dapagliflozin, a component of XIGDUO XR. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise [see Warnings and Precautions (5.7)].

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)

Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice [see Warnings and Precautions (5.9)].

Genital Mycotic Infections in Males (e.g., Balanitis)

Inform male patients that yeast infections of the penis (e.g., balanitis or balanoposthitis) may occur, especially in patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice [see Warnings and Precautions (5.9)].

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions (e.g., urticaria, anaphylactic reactions, and angioedema) have been reported with the components of XIGDUO XR. Advise patients to immediately report any signs or symptoms suggesting allergic reaction or angioedema, and to take no more of the drug until they have consulted prescribing physicians.

Pregnancy

Advise pregnant patients of the potential risk to a fetus with treatment with XIGDUO XR. Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant [see Use in Specific Populations (8.1)].

Lactation

Advise patients that use of XIGDUO XR is not recommended while breastfeeding [see Use in Specific Populations (8.2)].

Females and Males of Reproductive Potential

Inform female patients that treatment with metformin may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation [see Use in Specific Populations (8.3)].

Administration

Instruct patients that XIGDUO XR must be swallowed whole and not crushed or chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

Laboratory Tests

Due to the mechanism of action of dapagliflozin, patients taking XIGDUO XR will test positive for glucose in their urine.

Missed Dose

If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of XIGDUO XR at the same time.

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AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
10/19 US-33921 10/19
What is the most important information I should know about XIGDUO XR?

XIGDUO XR can cause serious side effects, including:

- **Lactic Acidosis.** Metformin, one of the medicines in XIGDUO XR, can cause a rare but serious condition called lactic acidosis (a build-up of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Call your healthcare provider right away if you have any of the following symptoms, which could be signs of lactic acidosis:

- you feel cold in your hands or feet
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you feel unusual sleepiness or sleep longer than usual
- you have stomach pains, nausea or vomiting

Most people who have had lactic acidosis with metformin have other things that, combined with the metformin use, led to the lactic acidosis. Tell your healthcare provider if you have any of the following, because you have a higher chance for getting lactic acidosis with XIGDUO XR if you:

- have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye.
- have liver problems.
- drink alcohol very often, or drink a lot of alcohol in short-term “binge” drinking.
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have surgery.
- have a heart attack, severe infection, or stroke.

The best way to keep from having a problem with lactic acidosis from metformin is to tell your healthcare provider if you have any of the problems in the list above. Your healthcare provider may decide to stop your XIGDUO XR for a while if you have any of these things. XIGDUO XR can have other serious side effects. See “What are the possible side effects of XIGDUO XR?”

What is XIGDUO XR?

- **XIGDUO XR** contains 2 prescription medicines called dapagliflozin (FARXIGA) and metformin HCl (GLUCOPHAGE). XIGDUO XR is used in adults with type 2 diabetes to:
  - improve blood sugar (glucose) control along with diet and exercise when treatment with either dapagliflozin or metformin has not controlled your blood sugar
  - reduce the risk of hospitalization for heart failure
- **XIGDUO XR** is not for people with type 1 diabetes.
- **XIGDUO XR** is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- It is not known if XIGDUO XR is safe and effective in children younger than 18 years of age.
Who should not take XIGDUO XR?

Do not take XIGDUO XR if you:
- have moderate to severe kidney problems or are on dialysis.
- are allergic to dapagliflozin, metformin HCl, or any of the ingredients in XIGDUO XR. See the end of this Medication Guide for a list of ingredients in XIGDUO XR. Symptoms of a serious allergic reaction to XIGDUO XR may include:
  - skin rash
  - raised red patches on your skin (hives)
  - swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing
If you have any of these symptoms, stop taking XIGDUO XR and contact your healthcare provider or go to the nearest hospital emergency room right away.
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in your blood or urine).

What should I tell my healthcare provider before taking XIGDUO XR?

Before you take XIGDUO XR, tell your healthcare provider if you:
- have type 1 diabetes or have had diabetic ketoacidosis
- have kidney problems.
- have liver problems.
- have a history of urinary tract infections or problems urinating.
- have heart problems, including congestive heart failure.
- are going to have surgery.
- are eating less due to illness, surgery or a change in your diet.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- drink alcohol very often, or drink a lot of alcohol in the short-term ("binge" drinking).
- are going to get an injection of dye or contrast agents for an x-ray procedure. XIGDUO XR may need to be stopped for a short time. Talk to your healthcare provider about when you should stop XIGDUO XR and when you should start XIGDUO XR again. See "What is the most important information I should know about XIGDUO XR?"
- are going to have surgery and will not be able to eat or drink much. XIGDUO XR will need to be stopped for a short time. Talk to your healthcare provider about when you should stop XIGDUO XR and when you should start XIGDUO XR again. See "What is the most important information I should know about XIGDUO XR?"
- are pregnant or plan to become pregnant. XIGDUO XR may harm your unborn baby. If you are pregnant or plan to become pregnant, talk to your healthcare provider about the best way to control your blood sugar
- are breastfeeding or plan to breastfeed. It is not known if XIGDUO XR passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby if you are taking XIGDUO XR

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

XIGDUO XR may affect the way other medicines work and other medicines may affect the way XIGDUO XR works. Especially tell your healthcare provider if you take:
- water pills (diuretics)
- rifampin (used to treat or prevent tuberculosis)
- phenytoin (used to control seizures)
- digoxin (used to treat heart problems)

Ask your healthcare provider for a list of these medicines if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.
How should I take XIGDUO XR?
• Take XIGDUO XR exactly as your healthcare provider tells you to take it.
• Do not change your dose of XIGDUO XR without talking to your healthcare provider.
• Take XIGDUO XR by mouth 1 time each day with meals to lower your chance of an upset stomach. Talk to your healthcare provider about the best time of day for you.
• Swallow XIGDUO XR whole. Do not crush, cut, or chew XIGDUO XR.
• You may sometimes pass a soft mass in your stools (bowel movement) that looks like XIGDUO XR tablets.
• When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine you need may change. Tell your healthcare provider right away if you have any of these conditions and follow your healthcare provider’s instructions.
• Stay on your prescribed diet and exercise program while taking XIGDUO XR.
• XIGDUO XR will cause your urine to test positive for glucose.
• Your healthcare provider may do certain blood tests before you start XIGDUO XR and during your treatment.
• Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your A1c.
• Follow your healthcare provider’s instructions for treating low blood sugar (hypoglycemia). Talk to your healthcare provider if low blood sugar is a problem for you.
• If you miss a dose of XIGDUO XR, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the medicine at the next regularly scheduled time.
• If you take too much XIGDUO XR, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking XIGDUO XR?
• Avoid drinking alcohol very often, or drinking a lot of alcohol in a short period of time ("binge" drinking). It can increase your chances of getting serious side effects.

What are the possible side effects of XIGDUO XR?
XIGDUO XR may cause serious side effects including:
See “What is the most important information I should know about XIGDUO XR?”
• Dehydration. XIGDUO XR can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). You may be at a higher risk of dehydration if you:
  ○ have low blood pressure
  ○ take medicines to lower your blood pressure, including water pills (diuretics)
  ○ are 65 years of age or older
  ○ are on a low salt diet
  ○ have kidney problems
Talk to your healthcare provider about what you can do to prevent dehydration including how much fluid you should drink on a daily basis.
• Ketoacidosis (increased ketones in your blood or urine). Ketoacidosis has happened in people who have type 1 diabetes or type 2 diabetes, during treatment with dapagliflozin, one of the medicines in XIGDUO XR. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Ketoacidosis may lead to death. Ketoacidosis can happen with XIGDUO XR even if your blood sugar is less than 250 mg/dL. Stop taking XIGDUO XR and call your healthcare provider right away if you get any of the following symptoms:
  ○ nausea
  ○ vomiting
  ○ stomach area (abdominal) pain
  ○ tiredness
  ○ trouble breathing
If you get any of these symptoms during treatment with XIGDUO XR, if possible check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.
• Kidney problems. Sudden kidney injury has happened to people taking XIGDUO XR. Call your healthcare provider right away if you:
  ○ reduce the amount of food or liquid you drink, for example, if you are sick and cannot eat or
  ○ you start to lose liquids from your body, for example, from vomiting, diarrhea, or being in the sun too long.
• **Serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking dapagliflozin, one of the medicines in XIGDUO XR. Tell your healthcare provider if you have any signs or symptoms of a urinary tract infection, such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.

• **Low blood sugar (hypoglycemia).** If you take XIGDUO XR with another medicine that can cause low blood sugar, such as sulfonylureas or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take XIGDUO XR. Signs and symptoms of low blood sugar may include:
  - headache
  - weakness
  - confusion
  - irritability
  - shaking or feeling jittery
  - sweating
  - dizziness
  - fast heartbeat

• **A rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has happened in women and men who take dapagliflozin, one of the medicines in XIGDUO XR. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries and may lead to death. **Seek medical attention immediately if you have fever or you are feeling very weak, tired or uncomfortable (malaise) and you develop any of the following symptoms in the area between and around the anus and genitals:**
  - pain or tenderness
  - swelling
  - redness of skin (erythema)

• **Low vitamin B₁₂ (vitamin B₁₂ deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B₁₂ in your blood, especially if you have had low vitamin B₁₂ levels before. Your healthcare provider may do blood tests to check your vitamin B₁₂ levels.

• **Vaginal yeast infection.** Women who take XIGDUO XR may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:
  - vaginal odor
  - white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
  - vaginal itching

• **Yeast infection of the penis (balanitis).** Men who take XIGDUO XR may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:
  - redness, itching, or swelling of the penis
  - rash of the penis
  - foul smelling discharge from the penis
  - pain in the skin around the penis

Talk to your healthcare provider about what to do if you get symptoms of a yeast infection of the vagina or penis. Your healthcare provider may suggest you use an over-the-counter antifungal medicine. Talk to your healthcare provider right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

**The most common side effects of XIGDUO XR include:**
- vaginal yeast infections and yeast infections of the penis
- diarrhea
- headache
- stuffy or runny nose and sore throat
- urinary tract infection

Tell your healthcare provider or pharmacist if you have any side effect that bothers you or does not go away.

These are not all of the possible side effects of XIGDUO XR. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

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**How should I store XIGDUO XR?**
Store XIGDUO XR at room temperature between 68°F and 77°F (20°C and 25°C).
**Keep XIGDUO XR and all medicines out of the reach of children.**
General information about the safe and effective use of XIGDUO XR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XIGDUO XR for a condition for which it is not prescribed. Do not give XIGDUO XR to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about XIGDUO XR. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about XIGDUO XR that is written for healthcare professionals.

For more information, go to www.xigduoxr.com or call 1-800-236-9933

What are the ingredients of XIGDUO XR?

Active ingredients: dapagliflozin and metformin hydrochloride

Inactive ingredients: microcrystalline cellulose, lactose anhydrous, crospovidone, silicon dioxide, magnesium stearate, carboxymethylcellulose sodium, and hypromellose.

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 2.5 mg/1000 mg, 5 mg/1000 mg, 10 mg/500 mg, and 10 mg/1000 mg tablets contains iron oxides.

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