HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XIGDUO XR safely and effectively. See full prescribing information for XIGDUO XR.

XIGDUO® XR (dapagliflozin and metformin HCl extended-release) tablets, for oral use
Initial U.S. Approval: 2014

WARNING: LACTIC ACIDOSIS
See full prescribing information for complete boxed warning.

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. (5.1)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, 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. (5.1)**
- **If lactic acidosis is suspected, discontinue XIGDUO XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.7) 10/2018

---------- INDICATIONS AND USAGE ----------
XIGDUO XR is a combination of dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate. (1)

Limitation of use:
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1.1)

---------- DOSAGE AND ADMINISTRATION ----------
- Individualize the starting dose based on the patient's current treatment. (2.1)
- Administer once daily in the morning with food. (2.1)
- Swallow whole. Never crush, cut, or chew. (2.1)
- For patients not already taking dapagliflozin, the recommended starting dose for dapagliflozin is 5 mg once daily. (2.1)
- For patients requiring a dose of 5 mg dapagliflozin and 2000 mg metformin HCl extended-release, use two of the 2.5 mg/1000 mg metformin HCl extended-release tablets. (2.1)
- Do not exceed a daily dose of 10 mg dapagliflozin/2000 mg metformin HCl extended-release. (2.1)
- Assess renal function before initiating. Do not initiate or continue if eGFR is below 60 mL/min/1.73 m^2. (2.2, 4)
- No dosage adjustment is indicated in patients with mild renal impairment. (2.2)
- XIGDUO XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
- 2.5 mg dapagliflozin/1000 mg metformin HCl extended-release (3)
- 5 mg dapagliflozin/500 mg metformin HCl extended-release (3)
- 5 mg dapagliflozin/1000 mg metformin HCl extended-release (3)
- 10 mg dapagliflozin/500 mg metformin HCl extended-release (3)
- 10 mg dapagliflozin/1000 mg metformin HCl extended-release (3)

---------- CONTRAINDICATIONS ----------
- Moderate to severe renal impairment: (eGFR below 60 mL/min/1.73 m^2), end-stage renal disease or dialysis. (4, 5.1)
- History of serious hypersensitivity to dapagliflozin or hypersensitivity to metformin hydrochloride. (4, 6.1)
- Metabolic acidosis, including diabetic ketoacidosis. (4, 5.1)

---------- WARNINGS AND PRECAUTIONS ----------
- *Lactic acidosis*: See boxed warning (2.2, 4, 5.1)
- *Hypotension:* Before initiating XIGDUO XR, assess volume status and correct hypovolemia in the elderly, in 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 and Impairment in renal function:* 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, institute prompt treatment. (5.7)
- *Vitamin B_{12} deficiency:* Metformin may lower vitamin B_{12} levels. Measure hematological parameters annually. (5.8, 6.1)
- *Genital mycotic infections*: Monitor and treat if indicated. (5.9)
- *Increased LDL-C:* Monitor and treat per standard of care. (5.10)
- *Bladder Cancer:* An imbalance in bladder cancers was observed in clinical trials. Dapagliflozin should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer. (5.11)
- *Macrovascular outcomes:* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with XIGDUO XR. (5.12)

---------- 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 cimetidine) 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*: There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- *Nursing Mothers:* Discontinue XIGDUO XR or discontinue nursing. (8.3)
- *Geriatrics:* Higher incidence of adverse reactions related to reduced intravascular volume. Assess renal function more frequently. (5.1, 8.6)
- *Renal Impairment*: Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.1, 6.1, 8.6)
- *Hepatic Impairment*: Avoid use in patients with hepatic impairment. (8.7)

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LACTIC ACIDOSIS
1 INDICATIONS AND USAGE
1.1 Limitations of Use
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing
2.2 Patients with Renal Impairment
2.3 Discontinuation for Iodinated Contrast Imaging Procedures
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Lactic Acidosis
5.2 Hypotension
5.3 Ketoacidosis
5.4 Acute Kidney Injury and Impairment in Renal Function
5.5 Urosepsis and Pyelonephritis
5.6 Use with Medications Known to Cause Hypoglycemia
5.7 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
5.8 Vitamin B_{12} Concentrations
5.9 Genital Mycotic Infections
5.10 Increases in Low-Density Lipoprotein Cholesterol (LDL-C)
5.11 Bladder Cancer
5.12 Macrovascular Outcomes
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Positive Urine Glucose Test
7.2 Interference with 1,5-anhydroglucitol (1,5-AG) Assay
7.3 Carbonic Anhydrase Inhibitors
7.4 Drugs that Reduce Metformin Clearance
7.5 Alcohol
7.6 Use with Other Drugs
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Mild Renal Impairment (eGFR ≥60 to <90 mL/min/1.73 m^2)
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Initial Combination Therapy with Metformin Extended-Release
14.2 Add-On to Metformin Immediate-Release
14.3 Active Glipizide-Controlled Study Add-On to Metformin Immediate-Release
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

***Sections or subsections omitted from the full prescribing information are not listed.**

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

1.1 Limitations of Use

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

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

- Healthcare providers should individualize the starting dose of XIGDUO XR based on the patient's current treatment *[see Dosage Forms and Strengths (3)]*.
- XIGDUO XR should be taken once daily in the morning with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin.
- XIGDUO XR tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of XIGDUO XR will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.
- For patients not already taking dapagliflozin, the recommended starting dose for dapagliflozin is 5 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.

Reference ID: 4341128

- 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.
- In patients with volume depletion, correcting this condition prior to initiation of XIGDUO XR is recommended *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5), and Patient Counseling Information (17)]*.

2.2 Patients with Renal Impairment

Assess renal function before initiating XIGDUO XR therapy and periodically thereafter.

XIGDUO XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 *[see Contraindications (4), Warnings and Precautions (5.1, 5.4), Adverse Reactions (6.1), and Use in Specific Populations (8.6)]*.

No dose adjustment for XIGDUO XR is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m^2 or greater).

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

- 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:

- Moderate to severe renal impairment (eGFR below 60 mL/min/1.73 m^2), end stage renal disease or patients on dialysis *[see Warnings and Precautions (5.1)]*.

Reference ID: 4341128

- History of a serious hypersensitivity reaction to dapagliflozin or hypersensitivity to metformin hydrochloride *[see Adverse Reactions (6.1)]*.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

5. WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis.

Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

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

In XIGDUO XR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute 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 (2.2) 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 60 mL/minute/1.73 m^2 *[see Contraindications (4)]*.
- Obtain an eGFR at least annually in all patients taking XIGDUO XR. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

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

Reference ID: 4341128

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients *[see Use in Specific Populations (8.5)]*.

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

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

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

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

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

5.2 Hypotension

Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating dapagliflozin *[see Adverse Reactions (6.1)]*, particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), 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 postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus taking sodium-glucose co transporter 2 (SGLT2) inhibitors, including dapagliflozin. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. XIGDUO XR is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1.1)]*.

Patients treated with XIGDUO XR who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of blood glucose levels as 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.

Reference ID: 4341128

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because 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 temporarily 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 and Impairment in Renal Function

Dapagliflozin causes intravascular volume contraction *[see Warning and Precautions (5.1)]*, and can cause renal impairment *[see Adverse Reactions (6.1)]*. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving dapagliflozin: some reports involved patients younger than 65 years of age.

Before initiating XIGDUO XR, 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 XIGDUO XR in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue XIGDUO XR promptly and institute treatment.

Dapagliflozin increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Adverse reactions related to renal function can occur after initiating XIGDUO XR *[see Adverse Reactions (6.1)]*. Renal function should be evaluated prior to initiation of XIGDUO XR and monitored periodically thereafter. XIGDUO XR is contraindicated in patients with an eGFR below 60 mL/min/1.73 m^2 *[see Dosage and Administration (2.2), 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 Use with Medications Known to Cause Hypoglycemia

Dapagliflozin

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

Reference ID: 4341128

Metformin hydrochloride

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs.

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 mellitus receiving SGLT2 inhibitors, including dapagliflozin. Cases have been reported in 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 B_{12} Concentrations

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. This decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on XIGDUO XR and any apparent abnormalities should be appropriately investigated and managed *[see Adverse Reactions (6.1)]*.

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful.

5.9 Genital Mycotic Infections

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

5.10 Increases in Low-Density Lipoprotein Cholesterol (LDL-C)

Increases in LDL-C occur with dapagliflozin *[see Adverse Reactions (6.1)]*. Monitor LDL-C and treat per standard of care after initiating XIGDUO XR.

5.11 Bladder Cancer

Across 22 clinical studies, newly diagnosed cases of bladder cancer were reported in 10/6045 patients (0.17%) treated with dapagliflozin and 1/3512 patient (0.03%) treated with placebo/comparator. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 4 cases with dapagliflozin and no cases with placebo/comparator. Bladder cancer risk factors and hematuria (a

Reference ID: 4341128

potential indicator of pre-existing tumors) were balanced between treatment arms at baseline. There were too few cases to determine whether the emergence of these events is related to dapagliflozin.

There are insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumors. Consequently, XIGDUO XR should not be used in patients with active bladder cancer. In patients with prior history of bladder cancer, the benefits of glycemic control versus unknown risks for cancer recurrence with XIGDUO XR should be considered.

5.12 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with XIGDUO XR.

6. ADVERSE REACTIONS

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

- Lactic Acidosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.2)]*
- Ketoacidosis *[see Warnings and Precautions (5.3)]*
- Acute Kidney Injury and Impairment in Renal Function *[see Warnings and Precautions (5.4)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.5)]*
- Use with Medications Known to Cause Hypoglycemia *[see Warnings and Precautions (5.6)]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.7)]*
- Vitamin B_{12} Concentrations *[see Warnings and Precautions (5.8)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.9)]*
- Increases in Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions (5.10)]*
- Bladder Cancer *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

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

Dapagliflozin and Metformin hydrochloride

Data from a prespecified pool of patients from 8 short-term, placebo-controlled studies of dapagliflozin coadministered with metformin immediate- or extended-release was used to evaluate safety. This pool included several add-on studies (metformin alone and in combination with a dipeptidyl peptidase-4 [DPP4] inhibitor and metformin, or insulin and metformin, 2 initial combination with metformin studies, and 2 studies of patients with cardiovascular disease [CVD] and type 2 diabetes 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.

Reference ID: 4341128

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

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

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

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

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, genital infection, vulvovaginitis, fungal genital infection, vulvovaginal candidiasis, vulval abscess, genital candidiasis, and vaginitis bacterial. (N for females: Placebo and metformin=534, dapagliflozin 5 mg and metformin=223, dapagliflozin 10 mg and metformin=430).

† Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, pyelonephritis, urethritis, and prostatitis.

Reference ID: 4341128

‡ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection, posthitis, balanoposthitis. (N for males: Placebo and metformin=651, dapagliflozin 5 mg and metformin=187, dapagliflozin 10 mg and metformin=553).

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

Metformin hydrochloride

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

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

Dapagliflozin

The data in Table 2 are derived from 12 placebo-controlled studies ranging from 12 to 24 weeks. In 4 studies dapagliflozin was used as monotherapy, and in 8 studies dapagliflozin was used as add-on to background antidiabetic therapy or as combination therapy with metformin *[see Clinical Studies (14)]*.

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

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

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

Adverse Reaction	**% of Patients**		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	**Dapagliflozin 5 mg N=1145**	**Dapagliflozin 10 mg N=1193**
Female genital mycotic infections*	1.5	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

Reference ID: 4341128

Adverse Reaction	% of Patients		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	Dapagliflozin 5 mg N=1145	Dapagliflozin 10 mg N=1193
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, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. (N for females: Placebo=677, dapagliflozin 5 mg=581, dapagliflozin 10 mg=598).

† Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia* urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

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

§ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, posthitis. (N for males: Placebo=716, dapagliflozin 5 mg=564, dapagliflozin 10 mg=595).

Pool of 13 Placebo-Controlled Studies for Dapagliflozin 10 mg

The safety and tolerability of 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 4% were older than 75 years. Fifty-eight percent (58%) of the population were male; 84% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 9 years, had a mean HbA1c of 8.2%, and 30% had established microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 m^2).

Volume Depletion

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

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

	Pool of 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies	
	Placebo	Dapagliflozin 5 mg	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg

Reference ID: 4341128

	Pool of 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies	
Overall population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)
Patient Subgroup n (%)					
Patients on loop diuretics	n=55 1 (1.8%)	n=40 0	n=31 3 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)
Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/1.73 m^2	n=107 2 (1.9%)	n=107 1 (0.9%)	n=89 1 (1.1%)	n=268 4 (1.5%)	n=265 5 (1.9%)
Patients ≥65 years of age	n=276 1 (0.4%)	n=216 1 (0.5%)	n=204 3 (1.5%)	n=711 6 (0.8%)	n=665 11 (1.7%)

* Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

Impairment of Renal Function

Use of dapagliflozin was associated with increases in serum creatinine and decreases in eGFR (see Table 4). In patients with normal or mildly impaired renal function at baseline, serum creatinine and eGFR returned to baseline values at Week 24. Renal-related adverse reactions, including renal failure and blood creatinine increase, were more frequent in patients treated with dapagliflozin (see Table 5). Elderly patients and patients with impaired renal function were more susceptible to these adverse reactions (see Table 5). Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2).

Table 4: Changes in Serum Creatinine and eGFR Associated with Dapagliflozin in the Pool of 12 Placebo-Controlled Studies and Moderate Renal Impairment Study

		Pool of 12 Placebo-Controlled Studies		
		Placebo N=1393	**Dapagliflozin 5 mg N=1145**	**Dapagliflozin 10 mg N=1193**
Baseline Mean	Serum Creatinine (mg/dL)	0.853	0.860	0.847
	eGFR (mL/min/1.73 m^2)	86.0	85.3	86.7
Week 1 Change	Serum Creatinine (mg/dL)	−0.003	0.029	0.041
	eGFR (mL/min/1.73 m^2)	0.4	−2.9	−4.1
Week 24 Change	Serum Creatinine (mg/dL)	−0.005	−0.001	0.001
	eGFR (mL/min/1.73 m^2)	0.8	0.8	0.3
		Moderate Renal Impairment Study		
		Placebo N=84	**Dapagliflozin 5 mg N=83**	**Dapagliflozin 10 mg N=85**
Baseline Mean	Serum Creatinine (mg/dL)	1.46	1.53	1.52
	eGFR (mL/min/1.73 m^2)	45.6	44.2	43.9
Week 1 Change	Serum Creatinine (mg/dL)	0.01	0.13	0.18
	eGFR (mL/min/1.73 m^2)	0.5	−3.8	−5.5
Week 24 Change	Serum Creatinine (mg/dL)	0.02	0.08	0.16
	eGFR (mL/min/1.73 m^2)	0.03	−4.0	−7.4

Reference ID: 4341128

Week 52 Change	Serum Creatinine (mg/dL)	0.10	0.06	0.15
	eGFR (mL/min/1.73 m^2)	−2.6	−4.2	−7.3

Table 5: Proportion of Patients with at Least One Renal Impairment-Related Adverse Reaction

	Pool of 6 Placebo-Controlled Studies (up to 104 weeks)*			Pool of 9 Placebo-Controlled Studies (up to 104 weeks)†	
Baseline Characteristic	**Placebo**	**Dapagliflozin 5 mg**	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**
Overall population Patients (%) with at least one event	n=785 13 (1.7%)	n=767 14 (1.8%)	n=859 16 (1.9%)	n=1956 82 (4.2%)	n=2026 136 (6.7%)
65 years of age and older Patients (%) with at least one event	n=190 4 (2.1%)	n=162 5 (3.1%)	n=159 6 (3.8%)	n=655 52 (7.9%)	n=620 87 (14.0%)
eGFR ≥30 and <60 mL/min/1.73 m^2 Patients (%) with at least one event	n=77 5 (6.5%)	n=88 7 (8.0%)	n=75 9 (12.0%)	n=249 40 (16.1%)	n=251 71 (28.3%)
65 years of age and older and eGFR ≥30 and <60 mL/min/1.73 m^2 Patients (%) with at least one event	n=41 2 (4.9%)	n=43 3 (7.0%)	n=35 4 (11.4%)	n=141 27 (19.1%)	n=134 47 (35.1%)

* Subset of patients from the pool of 12 placebo-controlled studies with long-term extensions.

† Subset of patients from the pool of 13 placebo-controlled studies with long-term extensions.

The safety of dapagliflozin was evaluated in a study of patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2). In this study 13 patients experienced bone fractures for treatment durations up to 104 weeks. No fractures occurred in the placebo group, 5 occurred in the dapagliflozin 5 mg group, and 8 occurred in the dapagliflozin 10 mg group. Eight of these 13 fractures were in patients who had a baseline eGFR of 30 to 45 mL/min/1.73 m^2. Eleven of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the anatomic site of fracture.

Hypoglycemia

The frequency of hypoglycemia by study *[see Clinical Studies (14)]* is shown in Table 6. Hypoglycemia was more frequent when dapagliflozin was added to sulfonylurea or insulin *[see Warnings and Precautions (5.6)]*.

Table 6: Incidence of Major* and Minor† Hypoglycemia in Placebo-Controlled Studies

	Placebo	**Dapagliflozin 5 mg**	**Dapagliflozin 10 mg**
Add-on to Metformin* (24 weeks)	**N=137**	**N=137**	**N=135**
Major [n (%)]	0	0	0

Reference ID: 4341128

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

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

† Minor episodes of hypoglycemia were defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL that does not qualify as a major episode.

‡ OAD = oral antidiabetic therapy.

Genital Mycotic Infections

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

Hypersensitivity Reactions

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

Laboratory Tests

Increase in Hematocrit

Reference ID: 4341128

Dapagliflozin

In the pool of 13 placebo-controlled studies, increases from baseline in mean hematocrit values were observed in dapagliflozin-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocrit were −0.33% in the placebo group and 2.30% in the dapagliflozin 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of dapagliflozin 10 mg–treated patients.

Increase in Serum Inorganic Phosphorus

Dapagliflozin

In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin 10 mg–treated patients compared with placebo-treated patients (mean increases of 0.13 mg/dL versus −0.04 mg/dL, respectively). Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥5.6 mg/dL if age 17-65 or ≥5.1 mg/dL if age ≥66) were reported in the dapagliflozin 10 mg group versus the placebo group at Week 24 (1.7% versus 0.9%, respectively).

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 change from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol and −1.0% versus 2.9% for LDL cholesterol in the placebo and dapagliflozin 10 mg groups, respectively.

Vitamin B_{12} Concentrations

Metformin hydrochloride

Metformin may lower serum vitamin B_{12} concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on XIGDUO XR and any apparent abnormalities should be appropriately investigated and managed *[see Warnings and Precautions (5.8)]*.

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 and Impairment in Renal Function
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Rash

Metformin hydrochloride

Reference ID: 4341128

- 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-anhydroglucitol (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 cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)]*. 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 Use with Other Drugs

Metformin hydrochloride

Some medications can predispose to hyperglycemia and may lead to loss of glycemic control. These medications include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving XIGDUO XR, the patient should be observed closely for loss of glycemic control. When such drugs are withdrawn from a patient receiving XIGDUO XR, the patient should be observed closely for hypoglycemia.

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

Reference ID: 4341128

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of XIGDUO XR or its individual components in pregnant women. Based on results of reproductive and developmental toxicity studies in animals, dapagliflozin, a component of XIGDUO XR, may affect renal development and maturation. In a juvenile rat study, increased incidence and/or severity of renal pelvic and tubular dilatations were evident at the lowest tested dose which was approximately 15 times clinical exposure from a 10 mg dose.

These outcomes occurred with drug exposures during periods of animal development that correlate with the late second and third trimesters of human pregnancy. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. XIGDUO XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dapagliflozin

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and renal pelvic and tubular dilatations were reported at all levels. Exposure at the lowest tested dose was 15 times the maximum clinical dose, based on AUC. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period. In a prenatal and postnatal development study, maternal rats were dosed from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415 times and 137 times, respectively, the human values at the clinical dose). Dose-related reductions in pup body weights were observed at doses ≥1 mg/kg/day (approximately ≥19 times the clinical dose). No adverse effects on developmental endpoints were noted at 1 mg/kg/day, or approximately 19 times the clinical dose.

In embryo-fetal development studies in rats and rabbits, dapagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities were observed in rabbits at any dose tested. In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day or 1441 times the maximum clinical dose of 10 mg. At higher doses in rats, malformations of blood vessels, ribs, vertebrae, manubria, and skeletal variations in fetuses at ≥150 mg/kg or 2344 times the 10 mg clinical dose were observed.

Metformin hydrochloride

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

Reference ID: 4341128

8.3 Nursing Mothers

It is not known whether XIGDUO XR is excreted in human milk. In studies performed with the individual components, both dapagliflozin (reaching levels 0.49 times that found in maternal plasma) and metformin are excreted in the milk of lactating rats.

Data in juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and in the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from dapagliflozin, a decision should be made whether to discontinue nursing or to discontinue XIGDUO XR, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

XIGDUO XR

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

Dapagliflozin

A total of 1424 (24%) of the 5936 dapagliflozin-treated patients were 65 years and over and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical safety and efficacy studies of dapagliflozin. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with dapagliflozin had adverse reactions related to volume depletion and renal impairment or failure compared to patients treated with placebo *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently than younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney and because the risk of lactic acidosis with metformin is greater in patients with moderately to severely impaired renal function. 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) and Clinical Pharmacology (12.3)]*.

8.6 Patients with Mild Renal Impairment (eGFR ≥60 to <90 mL/min/1.73 m^2)

Dapagliflozin

The pool of 21 double-blind, active- and placebo-controlled clinical safety and efficacy studies (dapagliflozin as monotherapy or in combination with other antidiabetic therapies) included 53% (4906/9339) of patients with mild renal impairment. The safety profile in patients with mild renal impairment is similar to that in the overall population.

Reference ID: 4341128

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 hydrochloride

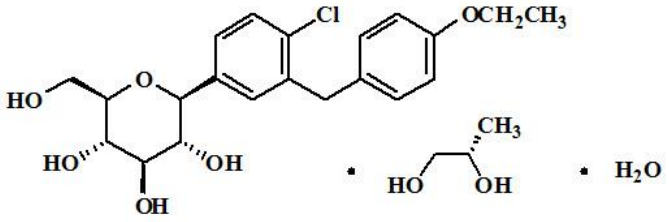
Overdose of metformin hydrochloride has occurred, including ingestion of amounts >50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose 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

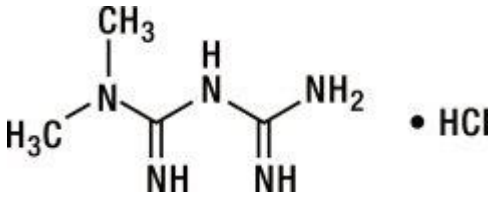
Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1*S*)-, compounded with (2*S*)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$ and the formula weight is 502.98. The structural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



Metformin hydrochloride

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

Reference ID: 4341128



XIGDUO XR

XIGDUO XR is available for oral administration as tablets containing the equivalent of 2.5 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin hydrochloride (XIGDUO XR 2.5mg/1000mg), 5 mg dapagliflozin as dapagliflozin propanediol and 500 mg metformin hydrochloride (XIGDUO XR 5 mg/500 mg), the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin hydrochloride (XIGDUO XR 5 mg/1000 mg), the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol and 500 mg metformin hydrochloride (XIGDUO XR 10 mg/500 mg), or the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin hydrochloride (XIGDUO XR 10 mg/1000 mg).

Each film-coated tablet of XIGDUO XR contains the following inactive ingredients: microcrystalline cellulose, 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. 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.

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 hydrochloride, 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.

Metformin hydrochloride

Metformin improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or in healthy subjects, except in unusual circumstances *[see Warnings and Precautions (5.6)]*, and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Reference ID: 4341128

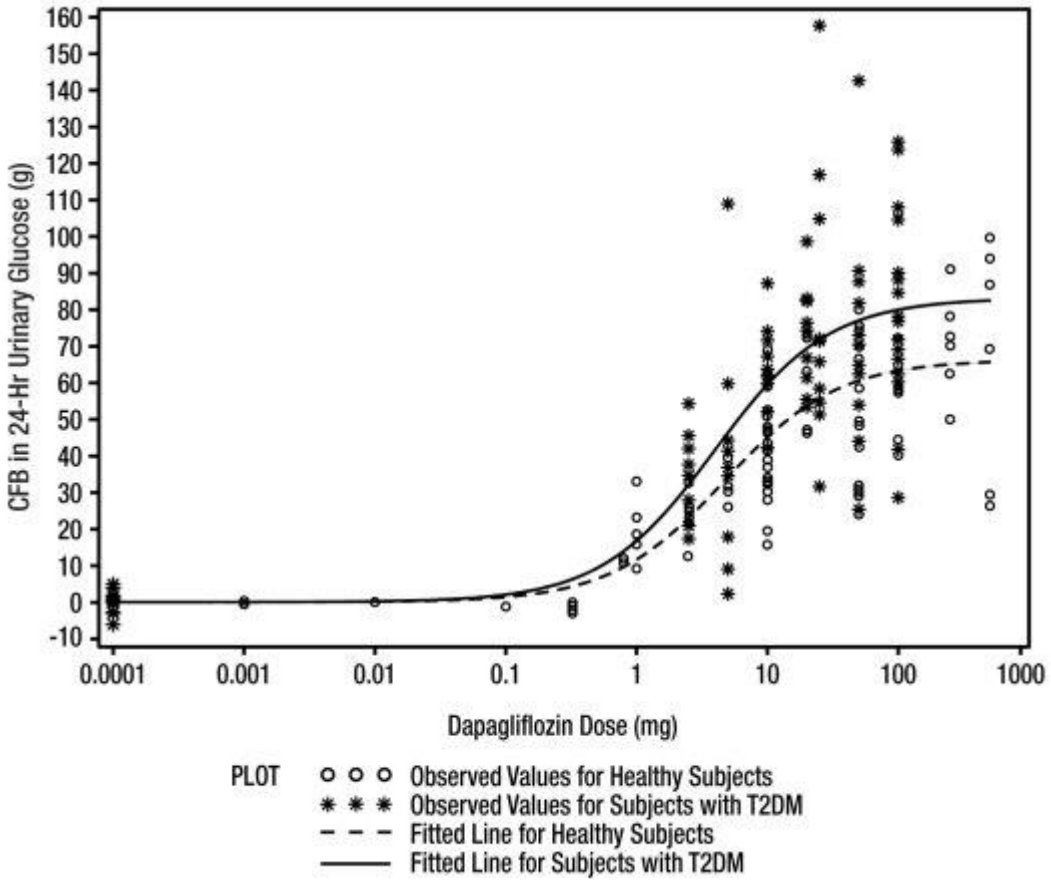
12.2 Pharmacodynamics

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 for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume *[see Adverse Reactions (6.1)]*.

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



Cardiac Electrophysiology

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

Reference ID: 4341128

12.3 Pharmacokinetics

XIGDUO XR

XIGDUO XR combination tablets are considered to be bioequivalent to coadministration of corresponding doses of dapagliflozin (FARXIGA®) and metformin hydrochloride extended-release (GLUCOPHAGE® XR) administered together as individual tablets.

The administration of XIGDUO XR in healthy subjects after a standard meal compared to the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin extended-release. Compared to the fasted state, the standard meal resulted in 35% reduction and a delay of 1 to 2 hours in the peak plasma concentrations of dapagliflozin. This effect of food is not considered to be clinically meaningful. Food has no relevant effect on the pharmacokinetics of metformin when administered as XIGDUO XR combination tablets.

Absorption

Dapagliflozin

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

Metformin hydrochloride

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

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metformin hydrochloride

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

Metabolism

Dapagliflozin

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-

Reference ID: 4341128

glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [^{14}C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

Metformin hydrochloride

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

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

Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [^{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. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life ($t_{½}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

Metformin hydrochloride

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

Specific Populations

Renal Impairment

Dapagliflozin

At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of dapagliflozin that were 45%, 2.04-fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than in patients with type 2 diabetes with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), and Use in Specific Populations (8.6)]*.

Metformin hydrochloride

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

Hepatic Impairment

Dapagliflozin

Reference ID: 4341128

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

Metformin hydrochloride

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

Geriatric

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 hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

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

Gender

Dapagliflozin

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

Metformin hydrochloride

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 hydrochloride

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

Reference ID: 4341128

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, 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 7 shows the effect of other coadministered drugs on metformin.

Table 7: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug (Dose Regimen)*	**Metformin (Dose Regimen)***	**Metformin**	
		Change† in AUC‡	**Change† in C_{max}**
No dosing adjustments required for the following:			
Glyburide (5 mg)	850 mg	↓9%§	↓7%§
Furosemide (40 mg)	850 mg	↑15%§	↑22%§
Nifedipine (10 mg)	850 mg	↑9%	↑20%
Propranolol (40 mg)	850 mg	↓10%	↓6%
Ibuprofen (400 mg)	850 mg	↑5%§	↑7%§
Drugs eliminated by renal tubular secretion may increase the accumulation of metformin *[see Drug Interactions (7.4)]*.			
Cimetidine (400 mg)	850 mg	↑40%	↑60%

* 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 8 shows the effect of metformin on other coadministered drugs.

Reference ID: 4341128

Table 8: Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug (Dose Regimen)*	Metformin (Dose Regimen)*	Coadministered Drug	
		Change† in AUC‡	Change† in C_{max}
No dosing adjustments required for the following:			
Glyburide (5 mg)	850 mg	↓22%§	↓37%§
Furosemide (40 mg)	850 mg	↓12%§	↓31%§
Nifedipine (10 mg)	850 mg	↑10%¶	↑8%
Propranolol (40 mg)	850 mg	↑1%¶	↑2%
Ibuprofen (400 mg)	850 mg	↓3%#	↑1%#
Cimetidine (400 mg)	850 mg	↓5%¶	↑1%

* 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 9 shows the effect of coadministered drugs on dapagliflozin. No dose adjustments are recommended for dapagliflozin.

Table 9: Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Dapagliflozin	
		Change† in AUC‡	Change† in C_{max}
No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	↓1%	↓7%
Pioglitazone (45 mg)	50 mg	0%	↑9%
Sitagliptin (100 mg)	20 mg	↑8%	↓4%
Glimepiride (4 mg)	20 mg	↓1%	↑1%
Voglibose (0.2 mg three times daily)	10 mg	↑1%	↑4%
Cardiovascular Agents			
Hydrochlorothiazide (25 mg)	50 mg	↑7%	↓1%
Bumetanide (1 mg)	10 mg once daily for 7 days	↑5%	↑8%
Valsartan (320 mg)	20 mg	↑2%	↓12%
Simvastatin (40 mg)	20 mg	↓1%	↓2%
Anti-infective Agent			
Rifampin (600 mg once daily for	10 mg	↓22%	↓7%

Reference ID: 4341128

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Dapagliflozin	
		Change† in AUC‡	Change† in C_{max}
No dosing adjustments required for the following:			
6 days)			
Non-Steroidal Anti-inflammatory Agent			
Mefenamic Acid (loading dose of 500 mg followed by 14 doses of 250 mg every 6 hours)	10 mg	↑51%	↑13%

* 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 10 shows the effect of dapagliflozin on other coadministered drugs. Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs.

Table 10: Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Coadministered Drug	
		Change† in AUC‡	Change† in C_{max}
No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	0%	↓5%
Pioglitazone (45 mg)	50 mg	0%	↓7%
Sitagliptin (100 mg)	20 mg	↑1%	↓11%
Glimepiride (4 mg)	20 mg	↑13%	↑4%
Cardiovascular Agents			
Hydrochlorothiazide (25 mg)	50 mg	↓1%	↓5%
Bumetanide (1 mg)	10 mg once daily for 7 days	↑13%	↑13%
Valsartan (320 mg)	20 mg	↑5%	↓6%
Simvastatin (40 mg)	20 mg	↑19%	↓6%
Digoxin (0.25 mg)	20 mg loading dose then 10 mg once daily for 7 days	0%	↓1%
Warfarin (25 mg) S-warfarin R-warfarin	20 mg loading dose then 10 mg once daily for 7 days	 ↑3% ↑6%	 ↑7% ↑8%

* Single dose unless otherwise noted.

Reference ID: 4341128

† 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 TOXICOLOGY

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/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/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 ≥100 μg/mL. Dapagliflozin was negative for clastogenicity in a series of *in vivo* studies evaluating micronuclei or DNA repair in rats at exposure multiples >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 ≤1708 and 998 times the maximum recommended human doses in males and females, respectively.

Metformin hydrochloride

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

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

Reference ID: 4341128

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 MRHD 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 hydrochloride extended-release (XR) tablets *[see Clinical Pharmacology (12.3)]*. Relative bioavailability studies between XIGDUO XR and coadministered dapagliflozin and metformin hydrochloride immediate-release (IR) tablets have not been conducted. The metformin hydrochloride XR tablets and metformin hydrochloride IR tablets have a similar extent of absorption (as measured by AUC), while peak plasma levels of XR tablets are approximately 20% lower than those of IR tablets at the same dose.

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

14.1 Initial Combination Therapy with Metformin Extended-Release

A total of 1241 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 the safety and efficacy of initial therapy with dapagliflozin 5 mg or 10 mg in combination with metformin XR formulation.

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

The combination treatment of dapagliflozin 10 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 11 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.

Reference ID: 4341128

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

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

* 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.

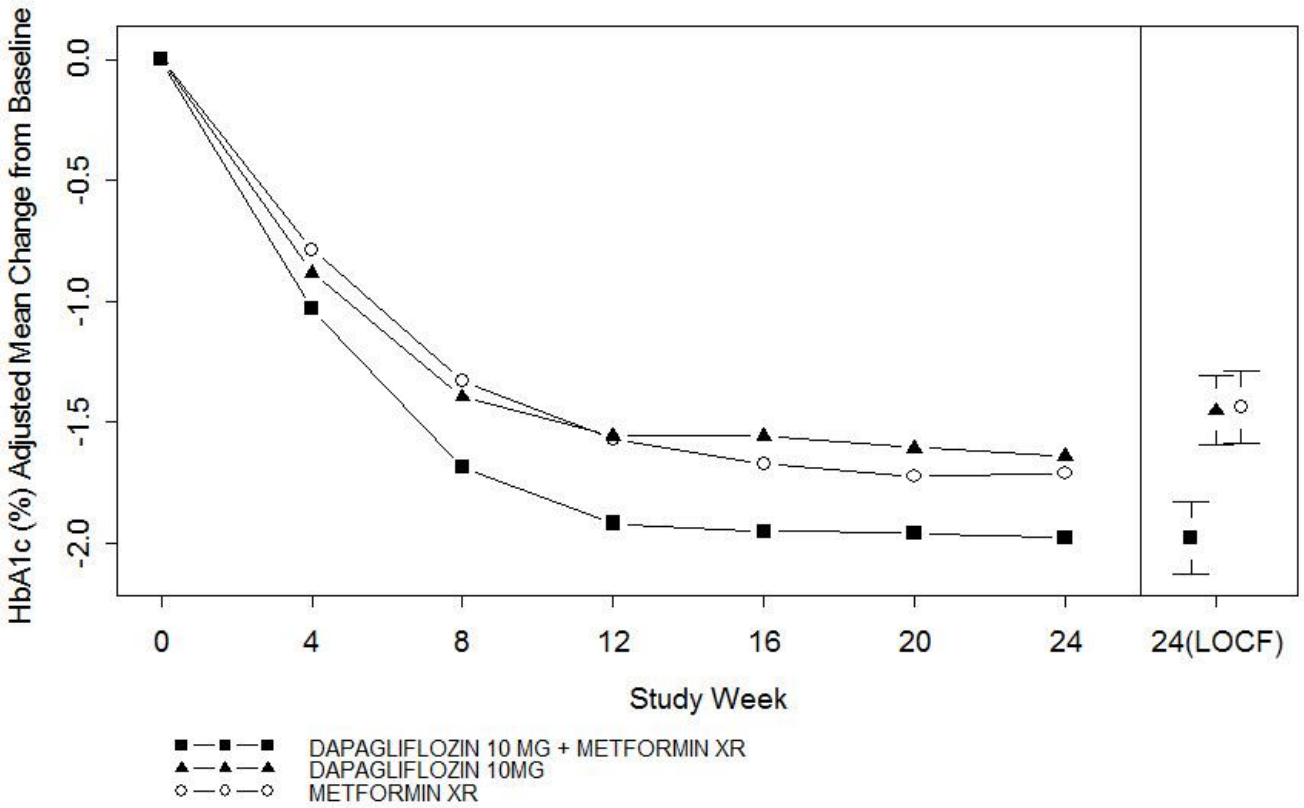
§ p-value <0.0001.

¶ Noninferior versus metformin XR.

\# p-value <0.05.

Reference ID: 4341128

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



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

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

The combination treatment of dapagliflozin 5 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 12).

Reference ID: 4341128

Table 12: Results at Week 24 (LOCF*) in an Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR

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

* 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.

14.2 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. 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.

Reference ID: 4341128

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 13 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 13: Results of a 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin

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

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

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

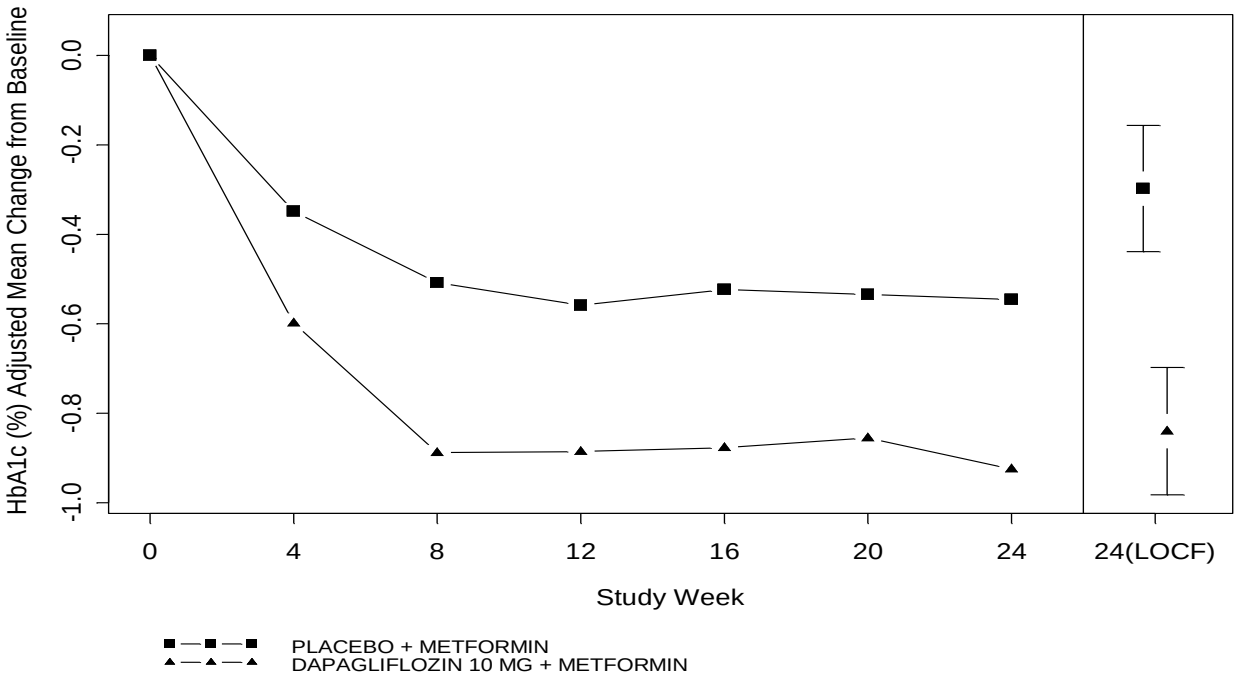
‡ Least squares mean adjusted for baseline value.

§ p-value <0.00001 versus placebo + metformin.

¶ p-value <0.05 versus placebo + metformin.

Reference ID: 4341128

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



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

14.3 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 as add-on therapy to metformin. Patients on metformin at a dose of at least 1500 mg/day were randomized following a 2-week placebo lead-in period to glipizide or dapagliflozin (5 or 2.5 mg, respectively) and were up-titrated over 18 weeks to optimal glycemic effect (FPG <110 mg/dL, <6.1 mmol/L) or to the highest dose level (up to glipizide 20 mg and dapagliflozin 10 mg) as tolerated by patients. Thereafter, doses were kept constant, except for down-titration to prevent hypoglycemia.

At the end of the titration period, 87% of patients treated with dapagliflozin had been titrated to the maximum study dose (10 mg) versus 73% treated with glipizide (20 mg). Dapagliflozin treatment led to a similar mean reduction in HbA1c from baseline at Week 52, compared with glipizide, thus demonstrating noninferiority (see Table 14). Dapagliflozin treatment led to a statistically significant mean reduction in body weight from baseline at Week 52 compared with a mean increase in body weight in the glipizide group. Statistically significant ($p<0.0001$) mean change from baseline in systolic blood pressure relative to glipizide plus metformin was −5.0 mmHg with dapagliflozin plus metformin.

Reference ID: 4341128

Table 14: Results at Week 52 (LOCF*) in an Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-On to Metformin

Efficacy Parameter	Dapagliflozin + Metformin N=400†	Glipizide + Metformin N=401†
HbA1c (%)		
Baseline (mean)	7.7	7.7
Change from baseline (adjusted mean‡)	−0.5	−0.5
Difference from glipizide + metformin (adjusted mean‡) (95% CI)	0.0§ (−0.1, 0.1)	
Body Weight (kg)		
Baseline (mean)	88.4	87.6
Change from baseline (adjusted mean‡)	−3.2	1.4
Difference from glipizide + metformin (adjusted mean‡) (95% CI)	−4.7¶ (−5.1, −4.2)	

* LOCF: last observation carried forward.
† Randomized and treated patients with baseline and at least 1 postbaseline efficacy measurement.
‡ Least squares mean adjusted for baseline value.
§ Noninferior to glipizide + metformin.
¶ p-value <0.0001.

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

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Pack Size	NDC Code
2.5/1000 mg	Light brown to brown, biconvex, oval-shaped	"1074" and "2.5/1000" debossed on one side and plain on the reverse side	Bottle of 60	0310-6225-60
5/500 mg	orange, biconvex, capsule-shaped	"1070" and "5/500" debossed on one side and plain on the reverse side	Bottle of 30 Bottle of 500	0310-6250-30 0310-6250-50
5/1000 mg	pink to dark pink, biconvex, oval-shaped	"1071" and "5/1000" debossed on one side and plain on the reverse side	Bottle of 30 Bottle of 60 Bottle of 90 Bottle of 400	0310-6260-30 0310-6260-60 0310-6260-90 0310-6260-40

Reference ID: 4341128

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Pack Size	NDC Code
10/500 mg	pink, biconvex, capsule-shaped	"1072" and "10/500" debossed on one side and plain on the reverse side	Bottle of 30 Bottle of 500	0310-6270-30 0310-6270-50
10/1000 mg	yellow to dark yellow, biconvex, oval-shaped	"1073" and "10/1000" debossed on one side and plain on the reverse side	Bottle of 30 Bottle of 90 Bottle of 400	0310-6280-30 0310-6280-90 0310-6280-40

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

See FDA-approved Patient Labeling (Medication Guide).

Instructions

Instruct patients to read the Medication Guide before starting treatment with XIGDUO XR and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of XIGDUO XR and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

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 (5.6)]*.

Instruct patient to immediately inform her healthcare provider if she is pregnant or plans to become pregnant. Based on animal data, XIGDUO XR may cause fetal harm in the second and third trimesters of pregnancy.

Instruct patient to immediately inform her healthcare provider if she is breastfeeding or planning to breastfeed. It is not known if XIGDUO XR is excreted in breast milk; however, based on animal data, XIGDUO XR may cause harm to nursing infants.

Inform patients that the most common adverse reactions associated with use of XIGDUO XR are female genital mycotic infections, nasopharyngitis, urinary tract infections, diarrhea, headache, nausea, and vomiting.

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.

Instruct patients to take XIGDUO XR only as prescribed. 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 2 tablets of XIGDUO XR at the same time, unless otherwise instructed by their healthcare provider.

Reference ID: 4341128

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 nonspecific 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 other 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 doctor 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 (5.2)]*. 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 (5.3)]*.

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 (5.5)]*.

Reference ID: 4341128

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 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.

Bladder Cancer

Inform patients to promptly report any signs of macroscopic hematuria or other symptoms potentially related to bladder cancer.

Laboratory Tests

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

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MEDICATION GUIDE
XIGDUO® XR (ZIG-DO-OH X-R)
(dapagliflozin and metformin HCL extended-release)
Tablets

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 doctor 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 doctor 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 doctor if you have any of the problems in the list above. Your doctor 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 along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes when treatment with either dapagliflozin or metformin has not controlled your blood sugar.
- 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).

Reference ID: 4341128

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 moderate to severe 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?"
- have or have had bladder cancer
- 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 or phenobarbital (used to control seizures)
- ritonavir (used to treat HIV infections)
- 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.
- 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 doctor 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 doctor 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. Talk to your doctor 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 doctor 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
  - shaking or feeling jittery
  - dizziness
  - weakness
  - sweating
  - fast heartbeat
  - confusion
  - drowsiness
  - irritability
  - hunger
- **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 B_{12} (vitamin B_{12} deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B_{12} in your blood, especially if you have had low vitamin B_{12} levels before. Your healthcare provider may do blood tests to check your vitamin B_{12} 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.
- **increased fats in your blood (bad cholesterol or LDL)**
- **bladder cancer.** In studies of dapagliflozin in people with diabetes, bladder cancer occurred in a few more people who were taking dapagliflozin than in people who were taking other diabetes medications. There were too few cases to know if bladder cancer was related to dapagliflozin. You should not take XIGDUO XR if you have bladder cancer. Tell your healthcare provider right away if you have any of the following symptoms:
  - blood or a red color in your urine
  - pain while you urinate

The most common side effects of XIGDUO XR include:

- vaginal yeast infections and yeast infections of the penis
- stuffy or runny nose and sore throat

- diarrhea
- headache
- nausea and vomiting

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 healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

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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