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----------

Boxed Warning	3/2017
Dosing and Administration (2.1)	7/2017
Warnings and Precautions (5)	3/2017

---------- 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)
- *Vitamin B_{12} deficiency*: Metformin may lower vitamin B_{12} levels. Measure hematological parameters annually. (5.7, 6.1)
- *Genital mycotic infections*: Monitor and treat if indicated. (5.8)
- *Increased LDL-C*: Monitor and treat per standard of care. (5.9)
- *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. (5.10)
- *Macrovascular outcomes*: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with XIGDUO XR. (5.11)

---------- 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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 7/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

***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.

- 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)*].

- 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.

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