

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use QTERNMET XR safely and effectively. See full prescribing information for QTERNMET XR.

**QTERNMET® XR (dapagliflozin, saxagliptin, and metformin hydrochloride) extended-release tablets, for oral use**  
Initial U.S. Approval: 2019

### 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 QTERNMET XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)

### INDICATIONS AND USAGE

QTERNMET XR is a sodium-glucose cotransporter 2 (SGLT2) inhibitor, a dipeptidyl peptidase-4 (DPP-4) inhibitor and a biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

#### Limitations of Use

- Is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)
- QTERNMET XR initiation is intended only for patients currently taking metformin. (1)

### DOSAGE AND ADMINISTRATION

- Assess renal function before initiation of therapy and periodically thereafter. (2.1)
- Individualize the starting total daily dose of QTERNMET XR based on the patient's current regimen, effectiveness, and tolerability. (2.2)
- Take QTERNMET XR orally, once daily in the morning with food. (2.2)
- For patients not currently taking dapagliflozin, the recommended starting total daily dose of QTERNMET XR is a 5 mg dapagliflozin/5 mg saxagliptin/1000 mg or 2000 mg metformin hydrochloride (HCl) once daily. (2.2)
- The maximum recommended daily dose is 10 mg dapagliflozin, 5 mg saxagliptin and 2000 mg metformin HCl. (2.2)
- Swallow tablet whole. Do not crush, cut or chew. (2.2)
- Discontinue QTERNMET XR at the time of, or prior to, an iodinated contrast imaging procedure. (2.5)

### DOSAGE FORMS AND STRENGTHS

- Tablet: 2.5 mg dapagliflozin/2.5 mg saxagliptin/1000 mg metformin HCl extended-release (3)
- Tablet: 5 mg dapagliflozin/2.5 mg saxagliptin/1000 mg metformin HCl extended-release (3)
- Tablet: 5 mg dapagliflozin/5 mg saxagliptin/1000 mg metformin HCl extended-release (3)
- Tablet: 10 mg dapagliflozin/5 mg saxagliptin/1000 mg metformin HCl extended-release (3)

### CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to dapagliflozin, saxagliptin, or metformin, including anaphylaxis, angioedema, or exfoliative skin conditions. (4, 5.9, 6.2)
- Moderate to severe renal impairment (eGFR <45 mL/min/1.73 m<sup>2</sup>), end-stage renal disease (ESRD), or patients on dialysis. (4)
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin. (4)

### WARNINGS AND PRECAUTIONS

**Lactic acidosis:** See boxed warning (2.2, 4, 5.1)

**Pancreatitis:** If pancreatitis is suspected, promptly discontinue. (5.2, 6.2)

**Heart Failure:** Consider the risks and benefits of QTERNMET XR in patients who have known risk factors for heart failure. Monitor patients. (5.3)

**Hypotension:** Before initiating QTERNMET XR, assess volume status and correct hypovolemia in the elderly, in patients with renal impairment or low systolic blood pressure, and in patients on loop diuretics. Monitor for signs and symptoms during therapy. (5.4, 6.1)

**Ketoacidosis:** Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue QTERNMET XR, evaluate and treat promptly. Before initiating QTERNMET XR, consider risk factors for ketoacidosis. Patients on QTERNMET XR may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.5, 6.2)

**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. (5.6, 6.2)

**Urosepsis and Pyelonephritis:** Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.7, 6.2)

**Hypoglycemia:** Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating QTERNMET XR in combination with these agents. (5.8, 6.1)

**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. (5.9)

**Hypersensitivity Reactions** (e.g., urticaria, facial edema): There have been postmarketing reports of serious hypersensitivity reactions treated with saxagliptin, such as anaphylaxis, angioedema, and exfoliative skin conditions. Promptly discontinue QTERNMET XR, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.10, 6.2)

**Vitamin B<sub>12</sub> deficiency:** Metformin may lower vitamin B<sub>12</sub> levels. Measure hematological parameters annually. (5.11, 6.1)

**Genital Mycotic Infections:** Monitor and treat if indicated. (5.12, 6.1)

**Increased LDL-C:** Monitor and treat per standard of care. (5.13, 6.1)

**Bladder Cancer:** An imbalance in bladder cancers was observed in clinical studies with dapagliflozin. QTERNMET XR 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. (5.14)

**Arthralgia:** Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.15, 6.1, 6.2)

**Bullous Pemphigoid:** There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue QTERNMET XR. (5.16)

**Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with QTERNMET XR. (5.17)

### ADVERSE REACTIONS

Adverse reactions reported in ≥5% of subjects treated with dapagliflozin and saxagliptin plus metformin were: upper respiratory tract infection, urinary tract infection, and dyslipidemia. (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](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

**Strong CYP3A4/5 Inhibitors** (e.g., Ketoconazole): Do not coadminister QTERNMET XR with strong cytochrome P450 3A4/5 inhibitors. (2.4, 7)

**Carbonic anhydrase inhibitors:** May increase the risk of lactic acidosis. Consider more frequent monitoring. (7)

**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)

**Alcohol:** Can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7)

----- **USE IN SPECIFIC POPULATIONS** -----

*Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)

*Lactation:* QTERNMET XR is not recommended when breastfeeding. (8.2)

*Females and Males of Reproductive Potential:* Advise premenopausal females of the potential for an unintended pregnancy. (8.3)

*Geriatrics:* Higher incidence of adverse reactions related to volume depletion and reduced renal function. (5.4, 5.6, 8.5)

*Renal Impairment:* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (2.2, 5.6, 6.1, 8.6)

*Hepatic Impairment:* Avoid use of QTERNMET XR in patients with clinical or laboratory evidence of hepatic impairment. (2.3, 8.7)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

**Revised: 5/2019**

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## FULL PRESCRIBING INFORMATION

### WARNING: LACTIC ACIDOSIS

- Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels ( $>5$  mmol/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 QTERNMET XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see [WARNINGS AND PRECAUTIONS \(5.1\)](#)].

## 1 INDICATIONS AND USAGE

QTERNMET XR (dapagliflozin, saxagliptin, and metformin hydrochloride) extended-release tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

### Limitations of Use

QTERNMET XR is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

QTERNMET XR initiation is intended only for patients currently taking metformin.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Prior to Initiation of QTERNMET XR

Assess renal function before initiating QTERNMET XR therapy and periodically thereafter [see [WARNINGS AND PRECAUTIONS \(5.1, 5.6\)](#) and [USE IN SPECIFIC POPULATIONS \(8.5, 8.6\)](#)].

In patients with volume depletion, correct this condition prior to initiation of QTERNMET XR [see [WARNINGS AND PRECAUTIONS \(5.4, 5.6\)](#) and [USE IN SPECIFIC POPULATIONS \(8.5, 8.6\)](#)].

## 2.2 Dosage

Individualize the starting total daily dose of QTERNMET XR based on the patient's current regimen, effectiveness, and tolerability [*see DOSAGE FORMS AND STRENGTHS (3)*].

Take QTERNMET XR orally, once daily in the morning with food.

For patients not currently taking dapagliflozin, the recommended starting total daily dose of QTERNMET XR is a 5 mg dapagliflozin/5 mg saxagliptin/1000 mg or 2000 mg metformin hydrochloride (HCl) extended-release once daily.

The maximum recommended daily dose is 10 mg dapagliflozin, 5 mg saxagliptin, and 2000 mg metformin HCl extended-release.

Swallow whole. Do not crush, cut or chew the QTERNMET XR tablet. Occasionally, the inactive ingredients of QTERNMET XR will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.

If a daily dose is missed and it is greater than or equal to 12 hours until the next dose, the dose should be taken. If a daily dose is missed and it is less than 12 hours until the next dose, the missed dose should be skipped and the next dose taken at the usual time.

## 2.3 Patients with Renal Impairment

No dose adjustment is needed in patients with an estimated glomerular filtration rate (eGFR) greater than or equal to 45 mL/min/1.73 m<sup>2</sup>.

QTERNMET XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m<sup>2</sup> [*see CONTRAINDICATIONS (4) and USE IN SPECIFIC POPULATIONS (8.6)*].

## 2.4 Use with Strong CYP3A4/5 Inhibitors

Do not coadminister QTERNMET XR with strong cytochrome P450 3A4/5 inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) [*see DRUG INTERACTIONS (7)*].

## 2.5 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue QTERNMET 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 QTERNMET XR if renal function is stable [*see WARNINGS AND PRECAUTIONS (5.1)*].

## 3 DOSAGE FORMS AND STRENGTHS

Extended-Release Tablets:

Dapagliflozin Strength	Saxagliptin Strength	Metformin HCl Strength	Color/Shape	Tablet Identifiers*
2.5 mg	2.5 mg	1000 mg	light brown to brown, biconvex, oval, film-coated tablet	3001
5 mg	2.5 mg	1000 mg	green, biconvex, oval, film-coated tablet	3002
5 mg	5 mg	1000 mg	pink, biconvex, oval, film-coated tablet	3003
10 mg	5 mg	1000 mg	gray, biconvex, oval, film-coated tablet	3004

\* Debossed on one side.

## 4 CONTRAINDICATIONS

QTERNMET XR is contraindicated in patients with:

- History of a serious hypersensitivity reaction to dapagliflozin, saxagliptin, or metformin, including anaphylaxis, angioedema, or exfoliative skin conditions [see [WARNINGS AND PRECAUTIONS \(5.10\)](#) and [ADVERSE REACTIONS \(6.1\)](#)].
- Moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m<sup>2</sup>), end-stage renal disease (ESRD), or patients on dialysis [see [USE IN SPECIFIC POPULATIONS \(8.6\)](#)].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin [see [WARNINGS AND PRECAUTIONS \(5.1\)](#) and [ADVERSE REACTIONS \(6.1\)](#)].

## 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 QTERNMET XR.

In QTERNMET 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 QTERNMET 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 [see [DOSAGE AND ADMINISTRATION \(2.2\)](#) and [CLINICAL PHARMACOLOGY \(12.3\)](#)] based upon the patient's renal function include:

- Before initiating QTERNMET XR, obtain an estimated glomerular filtration rate (eGFR).
- Obtain an eGFR at least annually in all patients taking QTERNMET XR. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- QTERNMET XR is contraindicated in patients with an eGFR less than 45 mL/minute/1.73 m<sup>2</sup> [see [CONTRAINDICATIONS \(4\)](#), [USE IN SPECIFIC POPULATIONS \(8.6\)](#)].

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

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

*Radiological Studies with Contrast:* Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop QTERNMET 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 QTERNMET 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. QTERNMET 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 QTERNMET 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 QTERNMET 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 QTERNMET XR in patients with clinical or laboratory evidence of hepatic disease.

## **5.2 Pancreatitis**

There have been postmarketing reports of acute pancreatitis in patients taking saxagliptin. In a cardiovascular outcomes trial enrolling participants with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD (SAVOR trial), cases of definite acute pancreatitis were confirmed in 17 of 8240 (0.2%) patients receiving saxagliptin compared to 9 of 8173 (0.1%) receiving placebo. Pre-existing risk factors for pancreatitis were identified in 88% (15/17) of those patients receiving saxagliptin and in 100% (9/9) of those patients receiving placebo.

After initiation of QTERNMET XR, observe patients for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue QTERNMET XR and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using QTERNMET XR.

## **5.3 Heart Failure**

In a cardiovascular outcomes trial enrolling participants with established ASCVD or multiple risk factors for ASCVD (SAVOR trial), more patients randomized to saxagliptin (289/8280, 3.5%) were hospitalized for heart failure compared to patients randomized to placebo (228/8212, 2.8%). In a time-to-first-event analysis, the risk of hospitalization for heart failure was higher in the saxagliptin group (estimated Hazard Ratio: 1.27; 95% CI: 1.07, 1.51). Subjects with a prior history of heart failure and subjects with renal impairment had a higher risk for hospitalization for heart failure, irrespective of treatment assignment.

Consider the risks and benefits of QTERNMET XR prior to initiating treatment in patients at a higher risk of heart failure. Observe patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure



develops, evaluate and manage according to current standards of care and consider discontinuation of QTERNMET XR.

## 5.4 Hypotension

Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating QTERNMET XR [see [ADVERSE REACTIONS \(6.1\)](#)] particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m<sup>2</sup>), elderly patients or patients on loop diuretics. Before initiating QTERNMET XR, volume status should be assessed and corrected. QTERNMET XR is contraindicated in patients with an eGFR <45 mL/min/1.73 m<sup>2</sup>. Monitor for signs and symptoms of hypotension after initiating therapy.

## 5.5 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 receiving sodium glucose cotransporter-2 (SGLT2) inhibitors, including dapagliflozin. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. QTERNMET XR is not indicated for the treatment of patients with type 1 diabetes mellitus [see [INDICATIONS AND USAGE \(1\)](#)].

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

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

Before initiating QTERNMET 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 QTERNMET XR consider monitoring for ketoacidosis and temporarily discontinuing QTERNMET XR in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery) [see [ADVERSE REACTIONS \(6.2\)](#)].

## 5.6 Acute Kidney Injury and Impairment in Renal Function

Dapagliflozin causes intravascular volume contraction [see [WARNINGS AND PRECAUTIONS \(5.4\)](#)] 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 QTERNMET 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 and NSAIDs). Consider temporarily discontinuing QTERNMET 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 QTERNMET 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 QTERNMET XR [see [ADVERSE REACTIONS \(6.1\)](#)]. Renal function should be evaluated prior to initiation of QTERNMET XR and monitored periodically thereafter. QTERNMET XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m<sup>2</sup> [see [DOSAGE AND ADMINISTRATION \(2.2\)](#), [CONTRAINDICATIONS \(4\)](#) and [USE IN SPECIFIC POPULATIONS \(8.6\)](#)].

## **5.7 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 \(6.2\)](#)].

## **5.8 Hypoglycemia with Concomitant Use of Insulin or Insulin Secretagogues**

Insulin and insulin secretagogues, such as sulfonylureas, are known to cause hypoglycemia. Dapagliflozin, and saxagliptin can individually increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use but could occur during concomitant use with other glucose-lowering agents. Therefore, a lower dose of insulin or insulin secretagogue may be required to reduce the risk of hypoglycemia when these agents are used in combination with QTERNMET XR [see [ADVERSE REACTIONS \(6.1\)](#)].

## **5.9 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 QTERNMET 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 QTERNMET XR, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

### **5.10 Hypersensitivity Reactions**

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with saxagliptin. These reactions include anaphylaxis, angioedema and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with saxagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue QTERNMET XR, treat per standard of care, and monitor until signs and symptoms are resolved. Assess for other potential causes for the event. Institute alternative treatment for diabetes.

Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP-4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with saxagliptin.

### **5.11 Vitamin B<sub>12</sub> Concentrations**

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B<sub>12</sub> levels, without clinical manifestations, was observed in approximately 7% of patients. This decrease, possibly due to interference with B<sub>12</sub> absorption from the B<sub>12</sub>-intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B<sub>12</sub> supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on QTERNMET XR and any apparent abnormalities should be appropriately investigated and managed.

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

### **5.12 Genital Mycotic Infections**

Dapagliflozin increases the risks 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.

### **5.13 Increases in Low-Density Lipoprotein Cholesterol (LDL-C)**

Increases in LDL-C can occur with dapagliflozin [*see ADVERSE REACTIONS (6.1)*]. Monitor LDL-C and treat per standard of care after initiating QTERNMET XR.

### **5.14 Bladder Cancer**

Across 22 clinical studies for dapagliflozin, 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 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, QTERNMET 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 QTERNMET XR should be considered.

### **5.15 Severe and Disabling Arthralgia**

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate [see [ADVERSE REACTIONS \(6\)](#)].

### **5.16 Bullous Pemphigoid**

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving QTERNMET XR. If bullous pemphigoid is suspected, QTERNMET XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

### **5.17 Macrovascular Outcomes**

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

## **6 ADVERSE REACTIONS**

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

- Lactic Acidosis [see [BOXED WARNING](#) and [WARNINGS AND PRECAUTIONS \(5.1\)](#)]
- Pancreatitis [see [WARNINGS AND PRECAUTIONS \(5.2\)](#)]
- Heart Failure [see [WARNINGS AND PRECAUTIONS \(5.3\)](#)]
- Hypotension [see [WARNINGS AND PRECAUTIONS \(5.4\)](#)]
- Ketoacidosis [see [WARNINGS AND PRECAUTIONS \(5.5\)](#)]
- Acute Kidney Injury and Impairment in Renal Function [see [WARNINGS AND PRECAUTIONS \(5.6\)](#)]
- Urosepsis and Pyelonephritis [see [WARNINGS AND PRECAUTIONS \(5.7\)](#)]

- Hypoglycemia with Concomitant Use of Insulin or Insulin Secretagogues [see [WARNINGS AND PRECAUTIONS \(5.8\)](#)]
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) [see [WARNINGS AND PRECAUTIONS \(5.9\)](#)]
- Hypersensitivity Reactions [see [WARNINGS AND PRECAUTIONS \(5.10\)](#)]
- Vitamin B<sub>12</sub> Concentrations [see [WARNINGS AND PRECAUTIONS \(5.11\)](#)]
- Genital Mycotic Infections [see [WARNINGS AND PRECAUTIONS \(5.12\)](#)]
- Increases in Low-Density Lipoprotein Cholesterol (LDL-C) [see [WARNINGS AND PRECAUTIONS \(5.13\)](#)]
- Bladder Cancer [see [WARNINGS AND PRECAUTIONS \(5.14\)](#)]
- Severe and Disabling Arthralgia [see [WARNINGS AND PRECAUTIONS \(5.15\)](#)]
- Bullous Pemphigoid [see [WARNINGS AND PRECAUTIONS \(5.16\)](#)]

## 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 practice.

The safety of combined use of 10 mg dapagliflozin and 5 mg saxagliptin has been evaluated in adult subjects with type 2 diabetes in a pooled safety analysis of three phase 3 active/placebo-controlled clinical trials with a median exposure of 51 weeks. The pooled safety analysis included a total of 1169 adults: 492 patients in the combination of saxagliptin and dapagliflozin plus metformin group, 341 patients in the dapagliflozin plus metformin group, 336 patients the saxagliptin plus metformin group. The mean age of these subjects was 54 years, 0.8% were 75 years or older and 53.7% were female. The population was 80.9% White, 8.3% Black or African American, 3.7% Asian, and 6.6% Other race. At baseline the population had diabetes for an average of 7.5 years and a mean HbA1c of 8.4%. The mean eGFR at baseline was 94.4 mL/min/1.73 m<sup>2</sup>.

The common adverse reactions were based on the pooled analyses of these studies as shown in Table 1.

**Table 1: Adverse Reactions Reported in ≥2% of Subjects Treated with 10 mg Dapagliflozin and 5 mg Saxagliptin plus Metformin (≥1500 mg)**

Adverse Reaction Preferred Term*	Frequency %
Upper respiratory tract infection*	13.6
Urinary tract infection*	5.7
Dyslipidemia*	5.1

**Table 1: Adverse Reactions Reported in  $\geq 2\%$  of Subjects Treated with 10 mg Dapagliflozin and 5 mg Saxagliptin plus Metformin ( $\geq 1500$  mg)**

Adverse Reaction Preferred Term*	Frequency %
Headache	4.3
Diarrhea	3.7
Back pain	3.3
Genital infection*	3.0
Arthralgia	2.4

\* Adverse reactions that are medically related were grouped to a single preferred term.

Additionally, adverse reactions reported in  $<5\%$  and  $\geq 2\%$  from the dapagliflozin development program and  $\geq 1\%$  more frequently compared to placebo included increased urination and discomfort with urination.

#### *Metformin*

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.

#### Hypoglycemia

In the pooled analysis, the incidences of hypoglycemia (defined as blood glucose  $<54$  mg/dL regardless of the presence or absence of symptoms) and severe hypoglycemia (events requiring assistance due to neuroglycopenia, characterized by altered mental and/or physical status) were 1% and 0.2%, respectively.

#### Genital Mycotic Infections

Genital mycotic infections were reported in 15 subjects (3%) treated with combination plus metformin therapy. Reported adverse reactions by frequency included vulvovaginal mycotic infection, balanoposthitis, genital fungal infection, vaginal infection, and vulvovaginitis. The majority of subjects (84.2%) who experienced genital infection adverse reactions were females.

#### Urinary Tract Infections

Urinary tract infections were reported in 28 subjects (5.7%) treated with combination plus metformin therapy. Reported adverse reactions by frequency included urinary tract infection, Escherichia urinary tract infection, prostatitis, and pyelonephritis. The majority of subjects (80.6%) who experienced urinary tract infection adverse reactions were females.

## Volume Depletion

Dapagliflozin causes an osmotic diuresis, which may lead to reductions in intravascular volume. Events related to volume depletion (hypotension, dehydration, and hypovolemia) were reported in 2 subjects (0.4%) treated with dapagliflozin, saxagliptin and metformin combination therapy.

## Impairment of Renal Function

### *Dapagliflozin and Saxagliptin plus Metformin*

Adverse reactions related to decreased renal function were reported in 10 subjects (2.0%) treated with combination plus metformin therapy. The reported adverse reactions included decreased glomerular filtration rate, renal impairment, increased blood creatinine, acute renal failure, and decreased urine output. None of the adverse reactions were reported as serious and all but one were mild to moderate in intensity. Three subjects discontinued due to decreased eGFR. Subjects with AEs of renal impairment had lower mean eGFR values at baseline of 64.4 mL/min/1.73 m<sup>2</sup> compared to 94.4 mL/min/1.73 m<sup>2</sup> in overall population treated with combination plus metformin therapy.

### *Dapagliflozin*

Use of dapagliflozin was associated with increases in serum creatinine and decreases in eGFR (see Table 2). 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 3). Elderly patients and patients with impaired renal function were more susceptible to these adverse reactions (see Table 3). Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m<sup>2</sup>). QTERNMET XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m<sup>2</sup>.

**Table 2: Changes in Serum Creatinine and eGFR Associated with Dapagliflozin in the Pool of 12 Placebo-Controlled Studies and Moderate Renal Impairment Studies**

		Pool of 12 Placebo-Controlled Studies		
		Placebo N=1393	5 mg Dapagliflozin N=1145	10 mg Dapagliflozin N=1193
Baseline Mean	Serum Creatinine (mg/dL)	0.853	0.860	0.847
	eGFR (mL/min/1.73 m <sup>2</sup> )	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 <sup>2</sup> )	0.4	-2.9	-4.1
Week 24 Change	Serum Creatinine (mg/dL)	-0.005	-0.001	0.001

**Table 2: Changes in Serum Creatinine and eGFR Associated with Dapagliflozin in the Pool of 12 Placebo-Controlled Studies and Moderate Renal Impairment Studies**

	eGFR (mL/min/1.73 m <sup>2</sup> )	0.8	0.8	0.3
		<b>Moderate Renal Impairment Study*</b> (eGFR 30 to less than 60 mL/min/1.73 m <sup>2</sup> )		
		<b>Placebo N=84</b>	<b>5 mg Dapagliflozin N=83</b>	<b>10 mg Dapagliflozin N=85</b>
Baseline Mean	Serum Creatinine (mg/dL)	1.46	1.53	1.52
	eGFR (mL/min/1.73 m <sup>2</sup> )	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 <sup>2</sup> )	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 <sup>2</sup> )	0.03	-4.0	-7.4
Week 52 Change	Serum Creatinine (mg/dL)	0.10	0.06	0.15
	eGFR (mL/min/1.73 m <sup>2</sup> )	-2.6	-4.2	-7.3
		<b>Moderate Renal Impairment Study</b> (eGFR 45 to less than 60 mL/min/1.73 m <sup>2</sup> )		
		<b>Placebo N=161</b>	<b>10 mg Dapagliflozin N=160</b>	
Baseline Mean	Serum Creatinine (mg/dL)	1.25	1.25	
	eGFR (mL/min/1.73 m <sup>2</sup> )	53.6	53.3	
Week 4 Change	Serum Creatinine (mg/dL)	-0.02	0.09	
	eGFR (mL/min/1.73 m <sup>2</sup> )	1.3	-3.8	
Week 12 Change	Serum Creatinine (mg/dL)	-0.02	0.08	
	eGFR (mL/min/1.73 m <sup>2</sup> )	1.5	-3.2	
Week 24 Change	Serum Creatinine (mg/dL)	-0.003	0.06	



**Table 2: Changes in Serum Creatinine and eGFR Associated with Dapagliflozin in the Pool of 12 Placebo-Controlled Studies and Moderate Renal Impairment Studies**

	eGFR (mL/min/1.73 m <sup>2</sup> )	0.8	-2.0
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\* QTERN is contraindicated in patients with an eGFR <45 mL/min/1.73 m<sup>2</sup>.

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

‡ QTERNMET XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m<sup>2</sup>.

In the pool of 12 clinical studies, a subgroup analysis assessed the safety of patients with eGFR between 30 to less than 60 mL/min/1.73 m<sup>2</sup>. At Week 24, the safety of dapagliflozin was similar to that seen in the dapagliflozin clinical program, although a higher proportion of patients had at least one event related to renal impairment or failure. QTERNMET XR is contraindicated in patients with an eGFR <45 mL/min/1.73 m<sup>2</sup>.

### Fractures

In a study of patients with eGFR 30 to less than 60 mL/min/1.73 m<sup>2</sup>, 13 patients experienced bone fractures for treatment durations up to 104 weeks. No fractures occurred in the placebo group, 5 occurred in the 5 mg dapagliflozin group, and 8 occurred in the 10 mg dapagliflozin group. Eight of these 13

fractures were in patients who had a baseline eGFR of 30 to 45 mL/min/1.73 m<sup>2</sup>. QTERNMET XR is contraindicated in patients with an eGFR <45 mL/min/1.73 m<sup>2</sup>. Ten of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the anatomic site of fracture.

### Laboratory Findings

#### *Decrease in Lymphocyte Counts*

##### *Saxagliptin*

A dose-related mean decrease in absolute lymphocyte count has been observed with saxagliptin. In a pool of 5 placebo-controlled studies, a mean decrease in absolute lymphocyte count of approximately 100 cells/microL relative to placebo was observed. The proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 0.5%, 1.5%, and 0.4% in the 2.5 mg, 5 mg saxagliptin and placebo groups, respectively.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. The effect of saxagliptin on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

#### *Increase in Hematocrit*

##### *Dapagliflozin*

In a pool of 13 placebo-controlled studies with dapagliflozin, 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 10 mg dapagliflozin group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of 10 mg dapagliflozin -treated patients.

#### *Increase in Serum Inorganic Phosphorus*

##### *Dapagliflozin*

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

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

Patients treated with combination therapy demonstrated a mean percent increase from baseline LDL-cholesterol (ranging from 2.1 to 6.9%).

### Elevations in Creatine Kinase

An imbalance in the number of subjects who experienced serum creatine kinase (CK) elevations >10x the upper limit of normal (a marker of muscle injury/necrosis) was observed in 5 subjects (1%) treated with combination therapy. The elevations were transient. Rhabdomyolysis was reported for one of those subjects for which no obvious cause was identified.

### Decrease in Serum Bicarbonate

In a study of concomitant therapy of 10 mg dapagliflozin with exenatide extended-release (on a background of metformin), four patients (1.7%) on concomitant therapy had a serum bicarbonate value of less than or equal to 13 mEq/L compared to one each (0.4%) in the dapagliflozin and exenatide-extended release treatment groups [see [WARNINGS AND PRECAUTIONS \(5.5\)](#)].

### Vitamin B<sub>12</sub> Concentrations

#### *Metformin*

In clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B<sub>12</sub> levels was observed in approximately 7% of patients.

## **6.2 Postmarketing Experience**

Additional adverse reactions have been identified during post approval use of dapagliflozin, saxagliptin, and metformin. Because the following 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.

#### *Dapagliflozin*

- Ketoacidosis
- Acute Kidney Injury and Impairment in Renal Function
- Urosepsis and pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Rash

#### *Saxagliptin*

- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions
- Pancreatitis
- Severe and disabling arthralgia

- Bullous pemphigoid

### Metformin

- Cholestatic, hepatocellular, and mixed hepatocellular liver injury

## 7 DRUG INTERACTIONS

**Table 4: Clinically Relevant Interactions Affecting Drugs Coadministered with QTERNMET XR**

<b>Strong Inhibitors of CYP3A4/5 Enzymes</b>	
Clinical Impact	Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).
Intervention	Do not coadminister QTERNMET XR with strong cytochrome P450 3A4/5 inhibitors [see <a href="#">DOSAGE AND ADMINISTRATION (2.3)</a> and <a href="#">CLINICAL PHARMACOLOGY (12.3)</a> ].
<b>Carbonic Anhydrase Inhibitors</b>	
Clinical Impact	Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide, or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis.
Intervention	Concomitant use of these drugs with QTERNMET XR may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.
<b>Drugs that Reduce Metformin Clearance</b>	
Clinical Impact	Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2]/multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see <a href="#">CLINICAL PHARMACOLOGY (12.3)</a> ].
Intervention	Consider the benefits and risks of concomitant use.
<b>Alcohol</b>	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention	Warn patients against excessive alcohol intake while receiving QTERNMET XR.
<b>Insulin Secretagogues or Insulin</b>	
Clinical Impact	Dapagliflozin, and saxagliptin can individually increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Hypoglycemia does not occur in patients receiving metformin alone under

**Table 4: Clinically Relevant Interactions Affecting Drugs Coadministered with QTERNMET XR**

	usual circumstances of use but could occur during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin).
Intervention	A lower dose of insulin or insulin secretagogue may be required to reduce the risk of hypoglycemia when these agents are used in combination with QTERNMET XR.
<b>Drugs Affecting Glycemic Control</b>	
Clinical Impact	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 blockers, and isoniazid.
Intervention	When such drugs are administered to a patient or withdrawn from a patient receiving QTERNMET XR, the patient should be closely observed for loss of blood glucose control or hypoglycemia.
<b>Positive Urine Glucose Test</b>	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
<b>Interference with 1,5-anhydroglucitol (1,5-AG) Assay</b>	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

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

The limited available data with QTERNMET XR or components (dapagliflozin and saxagliptin) in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association

with metformin and major birth defect or miscarriage risk [see [Data](#)]. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see [Clinical Considerations](#)].

In animal studies, adverse renal pelvic and tubular dilatations, that were not fully reversible, were observed in rats when dapagliflozin (a component of QTERNMET XR) was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose [see [Data](#)].

No adverse developmental effects were observed when saxagliptin was administered to pregnant rats and rabbits [see [Data](#)].

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

### Clinical Considerations

#### *Disease-associated maternal and/or embryo-fetal risk*

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

### Data

#### *Human Data*

##### Metformin

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

#### *Animal Data*

##### *Dapagliflozin*

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

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

In embryo-fetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy. In rats, dapagliflozin was neither embryo-lethal nor teratogenic at doses up to 75 mg/kg/day (1441-times the 10 mg clinical dose, based on AUC). Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only at higher dosages, equal to or greater than 150 mg/kg (more than 2344-times the 10 mg clinical dose, based on AUC), which were associated with maternal toxicity. No developmental toxicities were observed in rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose, based on AUC).

#### *Saxagliptin and Metformin*

Saxagliptin and metformin coadministered to pregnant rats and rabbits during the period of organogenesis did not result in adverse developmental effects considered clinically relevant in either species. Doses tested in rats provided exposure up to 100- and 10-times clinical exposure, and doses tested in rabbits provided exposure up to 249- and 1-times clinical exposure relative to the clinical dose of 5 mg saxagliptin and 2000 mg metformin. Minor skeletal abnormalities associated with maternal toxicity were observed in rats. In rabbits, coadministration was poorly tolerated in a subset of mothers (12 of 30), resulting in death, moribundity, or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29, associated with fetal body weight decrements of 7%, and a low incidence of delayed ossification of the fetal hyoid bone.

#### *Saxagliptin*

In embryo-fetal development studies, saxagliptin was administered to pregnant rats and rabbits during the period of organogenesis, corresponding to the first trimester of human pregnancy. No adverse developmental effects were observed in either species at exposures 1503- and 152-times the 5 mg clinical dose in rats and rabbits, respectively, based on AUC. Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

In a prenatal and postnatal development study, no adverse developmental effects were observed in maternal rats administered saxagliptin from gestation Day 6 through lactation Day 21 at exposures up to 470-times the 5 mg clinical dose, based on AUC.

#### *Metformin*



Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

## 8.2 Lactation

### Risk Summary

There is limited information regarding the presence of QTERNMET XR or its components (dapagliflozin, saxagliptin, and metformin) in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk [*see Data*].

Dapagliflozin and saxagliptin are present in the milk of lactating rats [*see Data*]. However, due to species specific differences in lactation physiology, the clinical relevance of these data is not clear. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of QTERNMET XR is not recommended while breastfeeding.

### Data

#### *Dapagliflozin*

Dapagliflozin was present at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

#### *Saxagliptin*

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations.

#### *Metformin hydrochloride*

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

## 8.3 Females and Males of Reproductive Potential

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

## 8.4 Pediatric Use

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

## 8.5 Geriatric Use

Because metformin is eliminated by the kidney and because elderly patients are more likely to have decreased renal function, more frequent assessment of renal function is recommended in elderly patients [see [WARNINGS AND PRECAUTIONS \(5.1\)](#)].

### *Dapagliflozin*

A total of 1424 (24%) of the 5936 dapagliflozin-treated patients were 65 years and older and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical safety and efficacy studies of dapagliflozin. After controlling for level of renal function (eGFR), in clinical studies with dapagliflozin, efficacy was similar for patients under age 65 years and those 65 years and older. In patients 65 years and older, 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 \(5.3\)](#)].

### *Saxagliptin*

In the seven, double-blind, controlled clinical safety and efficacy trials of saxagliptin, a total of 4751 (42.0%) of the 11,301 patients randomized to saxagliptin were 65 years and over, and 1210 (10.7%) were 75 years and over. No overall differences in safety or effectiveness were observed between subjects  $\geq 65$  years old and younger subjects. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

### *Metformin hydrochloride*

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from 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. 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 [CONTRAINDICATIONS \(4\)](#), [WARNINGS AND PRECAUTIONS \(5.1\)](#), and [CLINICAL PHARMACOLOGY \(12.3\)](#)].

## 8.6 Renal Impairment

QTERNMET XR is contraindicated in patients with moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m<sup>2</sup>), ESRD, or on dialysis [see [DOSAGE AND ADMINISTRATION \(2.2\)](#), [CONTRAINDICATIONS \(4\)](#) and [WARNINGS AND PRECAUTIONS \(5.6\)](#)].

### *Dapagliflozin*

In clinical studies dapagliflozin was associated with increases in serum creatinine and decreases in eGFR [see [ADVERSE REACTIONS \(6.1\)](#)].

Dapagliflozin was evaluated in a study that included patients with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m<sup>2</sup>). The safety profile of dapagliflozin in the study of patients with an eGFR of 45 to less than 60 mL/min/1.73 m<sup>2</sup> was similar to the general population of patients with type 2 diabetes. Although patients in the dapagliflozin arm had reduction in eGFR compared to the placebo arm, eGFR generally returned towards baseline after treatment discontinuation.

### *Metformin*

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment.

## **8.7 Hepatic Impairment**

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. QTERNMET XR is not recommended in patients with hepatic impairment [see [CLINICAL PHARMACOLOGY \(12.3\)](#)].

## **10 OVERDOSAGE**

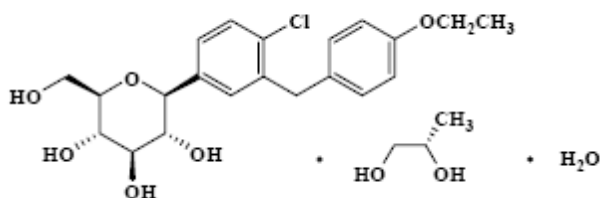
In the event of an overdose, contact the Poison Control Center. Appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

The removal of dapagliflozin by hemodialysis has not been studied. Saxagliptin and its major metabolite can be removed by hemodialysis (23% of dose over 4 hours). Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin 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.

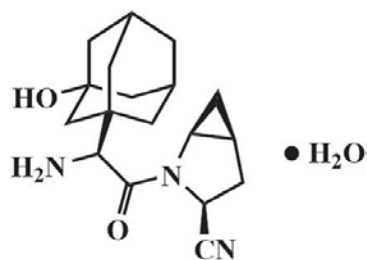
## **11 DESCRIPTION**

QTERNMET XR extended-release tablets for oral use contain dapagliflozin, saxagliptin and metformin HCl.

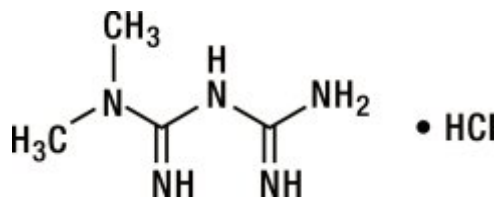
Dapagliflozin propanediol is an active inhibitor of sodium-glucose cotransporter 2 (SGLT2). It is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-. Dapagliflozin is compounded with (2S)-1,2-propanediol, hydrate (1:1:1) with an empirical formula as C<sub>21</sub>H<sub>25</sub>ClO<sub>6</sub>•C<sub>3</sub>H<sub>8</sub>O<sub>2</sub>•H<sub>2</sub>O and the molecular weight of 502.98. The structural formula is:



Saxagliptin is an active inhibitor of the dipeptidyl-peptidase-4 (DPP-4) enzyme. It is isolated in the monohydrate form chemically known as (1*S*,3*S*,5*S*)-2-[(2*S*)-2-amino-2-(3-hydroxytricyclo [3.3.1.1] dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1*S*,3*S*,5*S*)-2-[(2*S*)-2-amino-2-(3-hydroxy-1-adamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. The empirical formula is  $C_{18}H_{25}N_3O_2 \cdot H_2O$  and the molecular weight is 333.43. The structural formula is:



Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide. The molecular formula is  $C_4H_{11}N_5 \cdot HCl$  and the molecular weight is 165.63. The structural formula is:



QTERNMET XR is available as film-coated tablets of four strengths:

- 2.5 mg dapagliflozin/2.5 mg saxagliptin/1000 mg metformin HCl: Each tablet contains 2.5 mg dapagliflozin (equivalent to 3.08 mg dapagliflozin propanediol), 2.5 mg saxagliptin (exists in the form of HCl salt) and 1000 mg metformin HCl (equivalent to 779.86 mg metformin).
- 5 mg dapagliflozin/2.5 mg saxagliptin/1000 mg metformin HCl: Each tablet contains 5 mg dapagliflozin (equivalent to 6.15 mg dapagliflozin propanediol), 2.5 mg saxagliptin (exists in the form of HCl salt) and 1000 mg metformin HCl (equivalent to 779.86 mg metformin).
- 5 mg dapagliflozin/5 mg saxagliptin/1000 mg metformin HCl: Each tablet contains 5 mg dapagliflozin (equivalent to 6.15 mg dapagliflozin propanediol), 5 mg saxagliptin (exists in the form of HCl salt) and 1000 mg metformin HCl (equivalent to 779.86 mg metformin).

- 10 mg dapagliflozin/5 mg saxagliptin/1000 mg metformin HCl: Each tablet contains 10 mg dapagliflozin (equivalent to 12.3 mg dapagliflozin propanediol), 5 mg saxagliptin (exists in the form of HCl salt) and 1000 mg metformin HCl (equivalent to 779.86 mg metformin).

Each tablet also contains the following inactive ingredients: carboxymethyl cellulose sodium, croscopovidone, hypromellose 2208, iron oxides, lactose anhydrous, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, macrogol/polyethylene glycol, silicon dioxide, talc, and titanium dioxide. Hydrochloric acid and sodium hydroxide (if needed) are added for pH adjustment.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

QTERNMET XR contains: dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, saxagliptin, a dipeptidyl peptidase-4 (DPP-4) 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.

#### *Saxagliptin*

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the DPP-4 enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Saxagliptin is a competitive DPP-4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus.

#### *Metformin HCl*

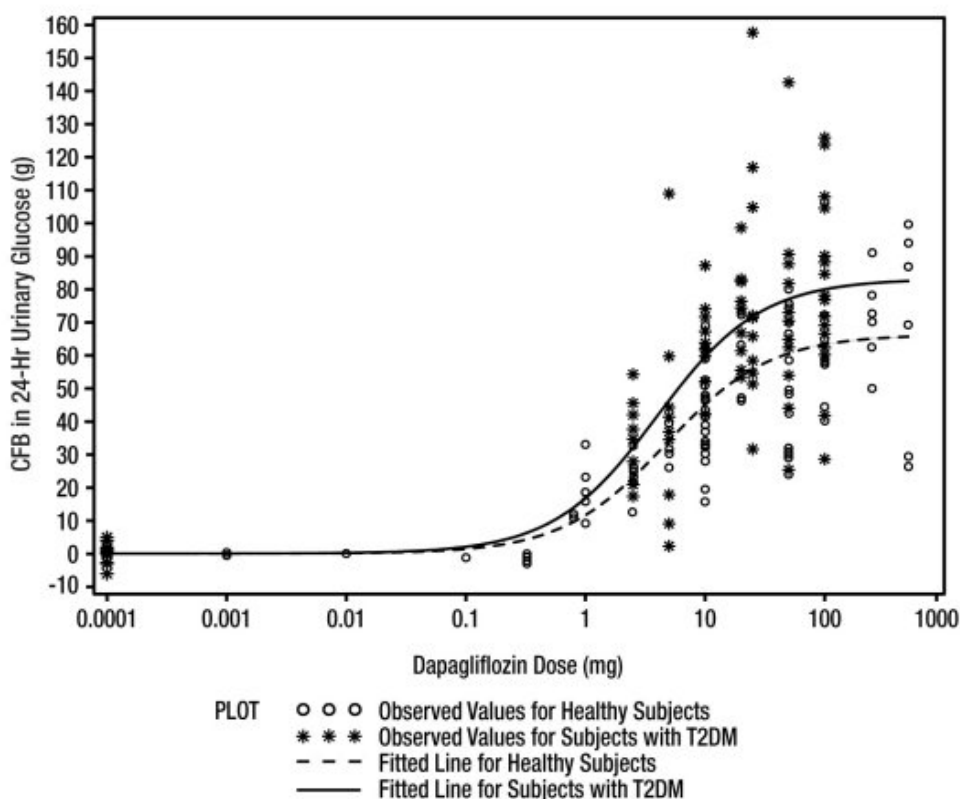
Metformin improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

### 12.2 Pharmacodynamics

#### *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. Dapagliflozin dose 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 at Week 12. 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)**



### *Saxagliptin*

In patients with type 2 diabetes mellitus, administration of saxagliptin inhibits DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent insulin secretion from pancreatic beta cells. The rise in insulin and decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

## Cardiac Electrophysiology

### *Dapagliflozin*

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended maximum 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 maximum daily dose) of dapagliflozin in healthy subjects.

### *Saxagliptin*

In a randomized, double-blind, placebo-controlled, 4-way crossover, active comparator study using moxifloxacin in 40 healthy subjects, saxagliptin was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 40 mg (8 times the recommended maximum daily dose).

## **12.3 Pharmacokinetics**

### *Dapagliflozin, Saxagliptin and Metformin HCl*

Overall, the pharmacokinetics of dapagliflozin, saxagliptin, and metformin were not affected in a clinically relevant manner when administered as QTERNMET XR.

### *Saxagliptin*

The pharmacokinetics of saxagliptin and its active metabolite, 5-hydroxy saxagliptin, were similar in healthy subjects and in patients with type 2 diabetes mellitus. The  $C_{max}$  and AUC values of saxagliptin and its active metabolite increased proportionally in the 2.5 to 400 mg dose range. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its active metabolite were 78 ng•h/mL and 214 ng•h/mL, respectively. The corresponding plasma  $C_{max}$  values were 24 ng/mL and 47 ng/mL, respectively. The average variability (%CV) for AUC and  $C_{max}$  for both saxagliptin and its active metabolite was less than 25%.

No appreciable accumulation of either saxagliptin or its active metabolite was observed with repeated once daily dosing at any dose level. No dose- and time-dependence were observed in the clearance of saxagliptin and its active metabolite over 14 days of once daily dosing with saxagliptin at doses ranging from 2.5 to 400 mg.

## 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 QTERNMET XR



with a standard meal decreases dapagliflozin  $C_{\max}$  by up to 39% and prolongs  $T_{\max}$  by up to 2 hours, but food does not alter AUC as compared with the fasted state.

### *Saxagliptin*

The median time to maximum concentration ( $T_{\max}$ ) following the 5 mg once daily dose was up to 2 hours for saxagliptin and 4 hours for its active metabolite. Administration of QTERNMET XR with a standard meal resulted in an increase in  $T_{\max}$  of saxagliptin by up to 1.5 h and an up to 16% decrease in saxagliptin  $C_{\max}$  as compared to fasted conditions. There was an up to 10% increase in the AUC of saxagliptin when given with a meal as compared to fasted conditions.

### *Metformin HCl*

Administration of QTERNMET XR with a standard meal resulted in an increase in  $T_{\max}$  of metformin by 2 h and no effect on metformin  $C_{\max}$  as compared to fasted conditions. There was an up to 15% increase in the AUC of saxagliptin when given with a meal as compared to fasted conditions. Both high and low-fat meals had the same effect on the pharmacokinetics of metformin extended-release.

Peak plasma levels of metformin extended-release tablets are approximately 20% lower compared to the same dose of metformin immediate-release tablets, however, the extent of absorption (as measured by AUC) is similar between extended-release tablets and immediate-release tablets.

At steady state, the AUC and  $C_{\max}$  are less than dose proportional for metformin extended-release within the range of 500 to 2000 mg. After repeated administration of metformin extended-release, metformin did not accumulate in plasma.

### Distribution

#### *Dapagliflozin*

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

#### *Saxagliptin*

The *in vitro* protein binding of saxagliptin and its active metabolite in human serum is negligible. Therefore, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

#### *Metformin HCl*

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  $654 \pm 358$  L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

### Metabolism

### *Dapagliflozin*

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

### *Saxagliptin*

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a DPP-4 inhibitor, which is one-half as potent as saxagliptin. Therefore, strong CYP3A4/5 inhibitors and inducers will alter the pharmacokinetics of saxagliptin and its active metabolite [see [DRUG INTERACTIONS \(7\)](#)].

### *Metformin HCl*

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 [<sup>14</sup>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 ( $t_{1/2}$ ) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

### *Saxagliptin*

Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of [<sup>14</sup>C]-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its active metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion. A total of 22% of the administered radioactivity was recovered in feces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract. Following a single oral dose of saxagliptin 5 mg to healthy subjects, the mean plasma terminal half-life ( $t_{1/2}$ ) for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.

### *Metformin HCl*

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

#### Effects of Age, Gender, Race, and Body Weight on Pharmacokinetics

Based on a population pharmacokinetic analysis, age, gender, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of dapagliflozin and saxagliptin.

#### 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 urinary 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 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 \(5.5\)](#) and [USE IN SPECIFIC POPULATIONS \(8.6\)](#)].

*Saxagliptin:* A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function. The 10 mg dosage is not an approved dosage. The degree of renal impairment did not affect C<sub>max</sub> of saxagliptin or its metabolite. In subjects with moderate renal impairment (eGFR 30 to less than 45 mL/min/1.73 m<sup>2</sup>), severe renal impairment (eGFR 15 to less than 30 mL/min/1.73 m<sup>2</sup>) and ESRD patient on hemodialysis, the AUC values of saxagliptin or its active metabolite were >2 fold higher than AUC values in subjects with normal renal function. QTERNMET XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m<sup>2</sup>, ESRD, or on dialysis.

*Metformin HCl:* In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased [see [CONTRAINDICATIONS \(4\)](#) and [WARNINGS AND PRECAUTIONS \(5.1\)](#)].

#### Hepatic Impairment

*Dapagliflozin:* In subjects with mild and moderate hepatic impairment (Child-Pugh classes A and B), mean C<sub>max</sub> 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.

*Saxagliptin:* In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean  $C_{\max}$  and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin. The 10 mg dosage is not an approved dosage. The corresponding  $C_{\max}$  and AUC of the active metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls. These differences are not considered to be clinically meaningful.

*Metformin HCl:* No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment [see [DOSAGE AND ADMINISTRATION \(2.3\)](#), [WARNINGS AND PRECAUTIONS \(5.1\)](#) and [USE IN SPECIFIC POPULATIONS \(8.7\)](#)].

### Pediatric

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

### Drug Interactions

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

### Dapagliflozin

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

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9).

In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, or 3A4, nor induced CYP 1A2, 2B6, or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter, and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

#### *Effects of Other Drugs on Dapagliflozin*

Table 5 shows the effect of coadministered drugs on the pharmacokinetics of dapagliflozin.

**Table 5: Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure**

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Dapagliflozin	
		Change <sup>†</sup> in AUC <sup>‡</sup>	Change <sup>†</sup> in C <sub>max</sub>
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%
Saxagliptin (5 mg single dose)	10 mg (single dose)	↓2%	↓6%
Cardiovascular Agents			
Hydrochlorothiazide (25 mg)	50 mg	↑7%	↓1%
Bumetanide (1 mg)	10 mg once daily for 7 days	↑5%	↑8%
Valsartan (320 mg)	20 mg	↑2%	↓12%
Simvastatin (40 mg)	20 mg	↓1%	↓2%
Anti-infective Agent			
Rifampin (600 mg once daily for 6 days)	10 mg	↓22%	↓7%
Non-Steroidal Anti-inflammatory Agent			
Mefenamic Acid (loading dose of 500 mg followed by 14 doses of 250 mg every 6 hours)	10 mg	↑51%	↑13%

\*Single dose unless otherwise noted.

<sup>†</sup> Percent change (with/without coadministered drug and no change=0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

<sup>‡</sup>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 6 shows the effect of dapagliflozin on other coadministered drugs. Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs.

**Table 6: Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs**

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Coadministered Drug	
		Change <sup>†</sup> in AUC <sup>‡</sup>	Change <sup>†</sup> in C <sub>max</sub>
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	0%	↓5%

**Table 6: Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs**

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Coadministered Drug	
		Change <sup>†</sup> in AUC <sup>‡</sup>	Change <sup>†</sup> in C <sub>max</sub>
Pioglitazone (45 mg)	50 mg	0%	↓7%
Sitagliptin (100 mg)	20 mg	↑1%	↓11%
Glimepiride (4 mg)	20 mg	↑13%	↑4%
<b>Cardiovascular Agents</b>			
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.

<sup>†</sup> Percent change (with/without coadministered drug and no change=0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

<sup>‡</sup> AUC=AUC(INF) for drugs given as single dose and AUC=AUC(TAU) for drugs given in multiple doses.

### Saxagliptin

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

The metabolism of saxagliptin is primarily mediated by CYP3A4/5.

In *in vitro* studies, saxagliptin and its active metabolite did not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, or 3A4. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is a P-glycoprotein (P-gp) substrate but is not a significant inhibitor or inducer of P-gp.

**Table 7: Effect of Coadministered Drugs on Systemic Exposures of Saxagliptin and its Active Metabolite, 5-hydroxy Saxagliptin**

Co-administered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Saxagliptin		
				Change <sup>†</sup> in AUC <sup>‡</sup>	Change <sup>†</sup> in C <sub>max</sub>
Metformin	1000 mg	100 mg	saxagliptin 5-hydroxy saxagliptin	↓2% ↓1%	↓21% ↓12%
Glyburide	5 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	↓2% ND	↑8% ND
Pioglitazone <sup>§</sup>	45 mg QD for 10 days	10 mg QD for 5 days	saxagliptin 5-hydroxy saxagliptin	↑11% ND	↑11% ND
Dapagliflozin	10 mg single dose	5 mg single dose	saxagliptin 5-hydroxy saxagliptin	↓1% ↑9%	↓7% ↑6%
Digoxin	0.25 mg q6h first day followed by q12h second day followed by QD for 5 days	10 mg QD for 7 days	saxagliptin 5-hydroxy saxagliptin	↑5% ↑6%	↓1% ↑2%
Simvastatin	40 mg QD for 8 days	10 mg QD for 4 days	saxagliptin 5-hydroxy saxagliptin	↑12% ↑2%	↑21% ↑8%
Diltiazem	360 mg LA QD for 9 days	10 mg	saxagliptin 5-hydroxy saxagliptin	↑109% ↓34%	↑63% ↓43%
Rifampin <sup>¶</sup>	600 mg QD for 6 days	5 mg	saxagliptin 5-hydroxy saxagliptin	↓76% ↑3%	↓53% ↑39%
Omeprazole	40 mg QD for 5 days	10 mg	saxagliptin 5-hydroxy saxagliptin	↑13% ND	↓2% ND
Aluminum hydroxide + magnesium hydroxide + simethicone	aluminum hydroxide: 2400 mg magnesium hydroxide: 2400 mg simethicone: 240 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	↓3% ND	↓26% ND
Famotidine	40 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	↑3% ND	↑14% ND
<b>Saxagliptin coadministered with strong CYP3A4/5 inhibitors [see <a href="#">DRUG INTERACTIONS (7)</a> and <a href="#">DOSAGE AND ADMINISTRATION (2.3)</a>]:</b>					
Ketoconazole	200 mg BID for 9 days	100 mg	saxagliptin 5-hydroxy saxagliptin	↑145% ↓88%	↑62% ↓95%
Ketoconazole	200 mg BID for 7 days	20 mg	saxagliptin 5-hydroxy saxagliptin	↑267% ND	↑144% ND



**Table 7: Effect of Coadministered Drugs on Systemic Exposures of Saxagliptin and its Active Metabolite, 5-hydroxy Saxagliptin**

Co-administered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Saxagliptin		
				Change <sup>†</sup> in AUC <sup>‡</sup>	Change <sup>†</sup> in C <sub>max</sub>

ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting.

\* Single dose unless otherwise noted.

<sup>†</sup> Percent change (with/without coadministered drug and no change=0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

<sup>‡</sup> AUC=AUC(INF) for drugs given as single dose and AUC=AUC(TAU) for drugs given in multiple doses.

<sup>§</sup> Results exclude one subject.

<sup>¶</sup> The plasma dipeptidyl peptidase-4 (DPP-4) activity inhibition over a 24-hour dose interval was not affected by rifampin.

#### *Effects of Saxagliptin on Other Drugs*

**Table 8: Effect of Saxagliptin on Systemic Exposures of Coadministered Drugs**

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Coadministered Drug		
				Change <sup>†</sup> in AUC <sup>‡</sup>	Change <sup>†</sup> in C <sub>max</sub>
Metformin	1000 mg	100 mg	metformin	↑20%	↑9%
Glyburide	5 mg	10 mg	glyburide	↑6%	↑16%
Pioglitazone <sup>§</sup>	45 mg QD for 10 days	10 mg QD for 5 days	pioglitazone hydroxy-pioglitazone	↑8% ND	↑14% ND
Digoxin	0.25 mg q6h first day followed by q12h second day followed by QD for 5 days	10 mg QD for 7 days	digoxin	↑6%	↑9%
Simvastatin	40 mg QD for 8 days	10 mg QD for 4 days	simvastatin simvastatin acid	↑4% ↑16%	↓12% 0%
Diltiazem	360 mg LA QD for 9 days	10 mg	diltiazem	↑10%	↑16%
Ketoconazole	200 mg BID for 9 days	100 mg	ketoconazole	↓13%	↓16%
Ethinyl estradiol and Norgestimate	ethinyl estradiol 0.035 mg and norgestimate	5 mg QD for 21 days	ethinyl estradiol norelgestromin norgestrel	↑7% ↑10% ↑13%	↓2% ↑9% ↑17%

**Table 8: Effect of Saxagliptin on Systemic Exposures of Coadministered Drugs**

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Coadministered Drug		
				Change <sup>†</sup> in AUC <sup>‡</sup>	Change <sup>†</sup> in C <sub>max</sub>
	0.250 mg for 21 days				

ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting.

\* 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.

§ Results include all subjects.

### Metformin

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

**Table 9: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure**

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Metformin	
			Change <sup>†</sup> in AUC <sup>‡</sup>	Change <sup>†</sup> in C <sub>max</sub>
Glyburide	5 mg	850 mg	↓9% <sup>§</sup>	↓7% <sup>§</sup>
Furosemide	40 mg	850 mg	↑15% <sup>§</sup>	↑22% <sup>§</sup>
Nifedipine	10 mg	850 mg	↑9%	↑20%
Propranolol	40 mg	850 mg	↓10%	↓6%
Ibuprofen	400 mg	850 mg	↑5% <sup>§</sup>	↑7% <sup>§</sup>
<b>Drugs eliminated by renal tubular secretion may increase the accumulation of metformin [see <a href="#">DRUG INTERACTIONS (7)</a>].</b>				
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.

**Table 10: Effect of Metformin on Coadministered Drug Systemic Exposure**

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Coadministered Drug	
			Change <sup>†</sup> in AUC <sup>‡</sup>	Change <sup>†</sup> in C <sub>max</sub>
Glyburide	5 mg	850 mg	↓22% <sup>§</sup>	↓37% <sup>§</sup>
Furosemide	40 mg	850 mg	↓12% <sup>§</sup>	↓31% <sup>§</sup>
Nifedipine	10 mg	850 mg	↑10% <sup>¶</sup>	↑8%
Propranolol	40 mg	850 mg	↑1% <sup>¶</sup>	↑2%
Ibuprofen	400 mg	850 mg	↓3% <sup>#</sup>	↑1% <sup>#</sup>
Cimetidine	400 mg	850 mg	↓5% <sup>¶</sup>	↑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.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### QTERNMET XR

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

#### Dapagliflozin

##### Carcinogenesis

Carcinogenicity was evaluated in 2-year studies conducted in CD-1 mice and Sprague-Dawley rats. Dapagliflozin did not increase the incidence of tumors in mice dosed orally at 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females (exposure less than or equal to 72-times (males) and 105-times (females) the 10 mg/day clinical dose, based on AUC). Dapagliflozin did not increase the incidence of tumors in rats (both males and females) dosed orally at 0.5, 2, and 10 mg/kg/day (exposure less than or equal to 131-times (males) and 186-times (females) the clinical dose of 10 mg/day, based on AUC).

##### Mutagenesis

Dapagliflozin was not mutagenic with or without metabolic activation in the Ames assay. Dapagliflozin was mutagenic in a series of *in vitro* clastogenicity assays at concentrations greater than or equal to 100 micrograms per mL but not without metabolic activation. Dapagliflozin was not mutagenic or clastogenic in a series of *in vivo* studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than 2100-times the clinical dose.

#### Impairment of Fertility

Dapagliflozin had no effects on the ability of rats to mate and sire, maintain a litter, or early embryonic development at exposure multiples less than or equal to 1708- and 998-times the maximum recommended human doses of 10 mg/day (based on AUC) in males and females, respectively.

#### Saxagliptin

##### Carcinogenesis

Carcinogenicity was evaluated in 2-year studies conducted in CD-1 mice and Sprague-Dawley rats. Saxagliptin did not increase the incidence of tumors in mice dosed orally at 50, 250, and 600 mg/kg up to 870-times (males) and 1165-times (females) the 5 mg/day clinical dose, based on AUC. Saxagliptin did not increase the incidence of tumors in rats dosed orally at 25, 75, 150, and 300 mg/kg up to 355-times (males) and 2217-times (females) the 5 mg/day clinical dose, based on AUC.

##### Mutagenesis

Saxagliptin was not mutagenic or clastogenic in a battery of genotoxicity tests (Ames bacterial mutagenesis, human and rat lymphocyte cytogenetics, rat bone marrow micronucleus and DNA repair assays). The active metabolite of saxagliptin was not mutagenic in an Ames bacterial assay.

#### Impairment of Fertility

Saxagliptin administered to rats had no effect on fertility or the ability to maintain a litter at exposures up to 603-times and 776-times the 5 mg clinical dose in males and females, based on AUC.

#### Metformin

##### Carcinogenesis

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

### Mutagenesis

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.

### Impairment of Fertility

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

## **13.2 Animal Toxicology and/or Pharmacology**

### Saxagliptin

Saxagliptin produced adverse skin changes in the extremities of cynomolgus monkeys (scabs and/or ulceration of tail, digits, scrotum, and/or nose). Skin lesions were reversible within exposure approximately 20-times the 5 mg clinical dose, but in some cases were irreversible and necrotizing at higher exposures. Adverse skin changes were not observed at exposures similar to (1- to 3-times) the 5 mg clinical dose. Clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

## **14 CLINICAL STUDIES**

Dapagliflozin and saxagliptin plus metformin has been studied in adult patients with type 2 diabetes mellitus (T2DM) inadequately controlled on metformin in the following studies.

Treatment with dapagliflozin and saxagliptin and metformin (combination or add-on therapy) at all doses produced statistically significant improvements in HbA1c compared to the active comparator or placebo study arms in combination with metformin.

### **14.1 Add-on Therapy with Dapagliflozin plus Saxagliptin in Patients on Metformin**

Adult patients with inadequately controlled type 2 diabetes participated in 2 active-controlled studies of 24-week duration to evaluate therapy with 5 mg dapagliflozin/5 mg saxagliptin or 10 mg dapagliflozin/5 mg saxagliptin combinations on a background of metformin.

One study was a 24-week randomized, double-blind, active-controlled, parallel group study (NCT02681094) in T2DM patients with an HbA1c  $\geq 7.5\%$  and  $\leq 10.0\%$ . Patients were on a stable dose of metformin HCl ( $\geq 1500$  mg per day) for at least 8 weeks prior to being randomized to one of three double-blind treatment groups to receive 5 mg dapagliflozin and 5 mg saxagliptin added to metformin, 5 mg saxagliptin and placebo added to metformin, or 5 mg dapagliflozin and placebo added to metformin.

At Week 24, concomitant addition of 5 mg dapagliflozin and 5 mg saxagliptin plus metformin resulted in statistically significant decreases in HbA1c, and a larger proportion of patients achieving the therapeutic

glycemic goal of HbA1c <7%, compared to dapagliflozin plus metformin or saxagliptin plus metformin (see Table 11).

**Table 11: HbA1c Results at Week 24 with the Combination of 5 mg Dapagliflozin and 5 mg Saxagliptin plus Metformin\***

Efficacy Parameter	5 mg Dapagliflozin and 5 mg Saxagliptin + Metformin		
	5 mg Dapagliflozin and 5 mg Saxagliptin + Metformin	5 mg Dapagliflozin + Metformin	5 mg Saxagliptin + Metformin
N <sup>†</sup>	290	289	291
Baseline (mean)	8.1	8.2	8.3
Change from baseline (adjusted mean) (95% CI)	-1.02 (-1.13, -0.90)	-0.62 (-0.73, -0.51)	-0.69 (-0.80, -0.59)
Difference from dapagliflozin + metformin (adjusted mean) (95% CI)	-0.40 <sup>‡</sup> (-0.55, -0.24)		
Difference from saxagliptin + metformin (adjusted mean) (95% CI)	-0.32 <sup>‡</sup> (-0.48, -0.17)		
Percent of patients achieving HbA1c <7%	42.8	21.8 <sup>§</sup>	28.5 <sup>¶</sup>

\* Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputation to model washout of the treatment effect using control arm data for all subjects having missing Week 24 data.

† The number of randomized subjects who took at least one dose of double-blind study medication and had a baseline value for HbA1c.

‡ p-value <0.0001.

§ p-value <0.0001 vs. dapagliflozin and saxagliptin plus metformin.

¶ p-value = 0.0018 vs. dapagliflozin and saxagliptin plus metformin.

The adjusted mean change from baseline for body weight at Week 24, using values regardless of rescue or treatment discontinuation, was -2.0 kg for the 5 mg dapagliflozin and 5 mg saxagliptin plus metformin group, -2.1 kg for the 5 mg dapagliflozin plus metformin group, and -0.4 kg for the 5 mg saxagliptin plus metformin group. The difference in mean body weight between the 5 mg dapagliflozin and 5 mg saxagliptin plus metformin group and the 5 mg dapagliflozin plus metformin group was -1.6 kg (95% CI [-2.1, -1.0]).

The second study was a 24-week randomized, double-blind, active comparator-controlled superiority study (NCT01606007) that compared once daily 10 mg dapagliflozin and 5 mg saxagliptin coadministered in combination with metformin XR with either 10 mg dapagliflozin and placebo added to

metformin or 5 mg saxagliptin and placebo added to metformin in T2DM adult patients with inadequate glycemic control on metformin alone (HbA1c  $\geq 8\%$  and  $\leq 12\%$ ).

At Week 24, concomitant addition of 10 mg dapagliflozin and 5 mg saxagliptin plus metformin resulted in statistically significant decreases in HbA1c, and a larger proportion of patients achieving an HbA1c  $< 7\%$ , compared to dapagliflozin plus metformin or saxagliptin plus metformin (see Table 12).

**Table 12: HbA1c Results at Week 24 with the Combination of 10 mg Dapagliflozin and 5 mg Saxagliptin plus Metformin\***

Efficacy Parameter	10 mg Dapagliflozin and 5 mg Saxagliptin + Metformin		
	10 mg Dapagliflozin and 5 mg Saxagliptin + Metformin	10 mg Dapagliflozin + Metformin	5 mg Saxagliptin + Metformin
N <sup>†</sup>	179	179	176
Baseline (mean)	8.9	8.9	9.0
Change from baseline (adjusted mean) (95% CI)	-1.49 (-1.64, -1.34)	-1.23 (-1.38, -1.08)	-1.00 (-1.15, -0.85)
Difference from dapagliflozin + metformin (adjusted mean) (95% CI)	-0.26 <sup>‡</sup> (-0.47, -0.05)		
Difference from saxagliptin + metformin (adjusted mean) (95% CI)	-0.49 <sup>§</sup> (-0.70, -0.27)		
Percent of patients achieving HbA1c $< 7\%$	40.2 <sup>¶</sup>	21.2 <sup>¶</sup>	16.5 <sup>¶</sup>

\* Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputation to model washout of the treatment effect using control arm data for all subjects having missing Week 24 data.

<sup>†</sup> The number of randomized subjects who took at least one dose of double-blind study medication and had a baseline value for HbA1c.

<sup>‡</sup> p-value=0.0148.

<sup>§</sup> p-value  $< 0.0001$ .

<sup>¶</sup> Not statistically significant based on the prespecified method for controlling type I error.

The adjusted mean change from baseline for body weight at Week 24, using values regardless of rescue or treatment discontinuation, was -2.0 kg for the 10 mg dapagliflozin and 5 mg saxagliptin plus metformin group, -2.3 kg for the 10 mg dapagliflozin plus metformin group, and 0 kg for the 5 mg saxagliptin plus metformin group.

## 14.2 Add-on Therapy with Saxagliptin in Patients on Dapagliflozin plus Metformin

A total of 315 patients with type 2 diabetes participated in this 24-week randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin added to dapagliflozin and

metformin in patients with a baseline of HbA1c  $\geq 7\%$  to  $\leq 10.5\%$  (NCT01619059). The mean age of these subjects was 54.6 years, 1.6% were 75 years or older, and 52.7% were female. The population was 87.9% White, 6.3% Black or African American, 4.1% Asian, and 1.6% Other race. At baseline the population had diabetes for an average of 7.7 years and a mean HbA1c of 7.9%. The mean eGFR at baseline was 93.4 mL/min/1.73 m<sup>2</sup>. Patients were required to be on a stable dose of metformin ( $\geq 1500$  mg per day) for at least 8 weeks prior to enrollment. Eligible subjects who completed the screening period entered the lead-in treatment period, which included 16 weeks of open-label metformin and 10 mg dapagliflozin treatment. Following the lead-in period, eligible patients were randomized to 5 mg saxagliptin (N=153) or placebo (N=162).

The group treated with add-on saxagliptin had statistically significant greater reductions in HbA1c from baseline versus the group treated with placebo (see Table 13).

**Table 13: HbA1c Change from Baseline at Week 24 in a Placebo-Controlled Trial of Saxagliptin as Add-on to Dapagliflozin and Metformin \***

Efficacy Parameter	5 mg Saxagliptin (N=153) <sup>†</sup>	Placebo (N=162) <sup>†</sup>
	In combination with Dapagliflozin and Metformin	
HbA1c (%) at week 24‡		
Baseline (mean)	8.0	7.9
Change from baseline (adjusted mean§)	−0.5	−0.2
95% Confidence Interval	(−0.6, −0.4)	(−0.3, −0.1)
Difference from placebo (adjusted mean)	−0.4¶	
95% Confidence Interval	(−0.5, −0.2)	
Percent of patients achieving HbA1c <7%	35.3	23.1

\* There were 6.5% (n=10) of randomized subjects in the saxagliptin arm and 3.1% (n=5) in the placebo arm for whom change from baseline HbA1c data was missing at Week 24. Of the subjects who discontinued study medication early, 9.1% (1 of 11) in the saxagliptin arm and 16.7% (1 of 6) in the placebo arm had HbA1c measured at Week 24.

<sup>†</sup> N is the number of randomized and treated patients.

<sup>‡</sup> Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputation to model washout of the treatment effect using placebo data for all subjects having missing Week 24 data.

<sup>§</sup> Least squares mean adjusted for baseline value.

<sup>¶</sup> p-value <0.0001.

### 14.3 Cardiovascular Safety Trial

The cardiovascular risk of saxagliptin was evaluated in SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in Myocardial Infarction), a multicenter, multinational, randomized, double-blind trial comparing saxagliptin (N=8280) to placebo



(N=8212), in adult patients with type 2 diabetes at high risk for atherosclerotic cardiovascular disease. Of the randomized study subjects, 97.5% completed the trial, and the median duration of follow-up was approximately 2 years (NCT01107886).

Subjects were at least 40 years of age, had HbA1c  $\geq 6.5\%$ , and multiple risk factors (21% of randomized subjects) for cardiovascular disease (age  $\geq 55$  years for men and  $\geq 60$  years for women plus at least one additional risk factor of dyslipidemia, hypertension, or current cigarette smoking) or established (79% of the randomized subjects) cardiovascular disease defined as a history of ischemic heart disease, peripheral vascular disease, or ischemic stroke. Overall, the use of diabetes medications was balanced across treatment groups (metformin 69%, insulin 41%, sulfonylureas 40%, and TZDs 6%). The use of cardiovascular disease medications was also balanced (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs] 79%, statins 78%, aspirin 75%, beta-blockers 62%, and non-aspirin antiplatelet medications 24%).

The majority of subjects were male (67%) and Caucasian (75%) with a mean age of 65 years. Approximately 16% of the population had moderate (eGFR  $\geq 30$  to  $\leq 50$  mL/min/1.73 m<sup>2</sup>) to severe (eGFR  $< 30$  mL/min/1.73 m<sup>2</sup>) renal impairment, and 13% had a prior history of heart failure. QTERNMET XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m<sup>2</sup>. Subjects had a median duration of type 2 diabetes mellitus of approximately 10 years and a mean baseline HbA1c level of 8.0%.

The primary analysis in SAVOR was time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event in SAVOR was defined as a cardiovascular death or a nonfatal myocardial infarction (MI) or a nonfatal ischemic stroke. The incidence rate of MACE was similar in both treatment arms: 3.8 MACE per 100 patient-years on placebo vs. 3.8 MACE per 100 patient-years on saxagliptin with an estimated HR: 1.0; 95.1% CI: (0.89, 1.12). The upper bound of this confidence interval, 1.12, excluded a risk margin larger than 1.3.

Vital status was obtained for 99% of subjects in the trial. There were 798 deaths in the SAVOR trial. Numerically more patients (5.1%) died in the saxagliptin group than in the placebo group (4.6%). The risk of deaths from all-cause mortality was not statistically different between the treatment groups (HR: 1.11; 95.1% CI: 0.96, 1.27).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

QTERNMET XR (dapagliflozin, saxagliptin, and metformin HCl) extended-release tablets are available in packages as listed:

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Pack Size	NDC Code
2.5 mg dapagliflozin /2.5 mg saxagliptin /1000 mg metformin HCl	Light brown to brown biconvex, oval	“3001” debossed on one side	Bottles of 60	0310-6925-60

<b>Tablet Strength</b>	<b>Film-Coated Tablet Color/Shape</b>	<b>Tablet Markings</b>	<b>Pack Size</b>	<b>NDC Code</b>
5 mg dapagliflozin /2.5 mg saxagliptin /1000 mg metformin HCl	Green biconvex, oval	“3002” debossed on one side	Bottles of 60	0310-6950-60
5 mg dapagliflozin /5 mg saxagliptin /1000 mg metformin HCl	Pink biconvex, oval	“3003” debossed on one side	Bottles of 30	0310-6975-30
10 mg dapagliflozin /5 mg saxagliptin /1000 mg metformin HCl	Gray biconvex, oval	“3004” debossed on one side	Bottles of 30	0310-6990-30

### Storage and Handling

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

## **17 PATIENT COUNSELING INFORMATION**

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

### **Lactic Acidosis**

- Inform patients of the risks of lactic acidosis due to the metformin component and its symptoms and conditions that predispose to its development [see [WARNINGS AND PRECAUTIONS \(5.1\)](#)]. Advise patients to discontinue QTERNMET 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 QTERNMET 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 QTERNMET XR.
- Inform patients about the importance of regular testing of renal function and hematological parameters when receiving treatment with QTERNMET XR.
- Instruct patients to inform their healthcare provider that they are taking QTERNMET XR prior to any surgical or radiological procedure, as temporary discontinuation of QTERNMET XR may be required until renal function has been confirmed to be normal [see [WARNINGS AND PRECAUTIONS \(5.1\)](#)].

## **Pancreatitis**

- Inform patients that acute pancreatitis has been reported during postmarketing use of saxagliptin. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis [*see* [WARNINGS AND PRECAUTIONS \(5.2\)](#)].
- Instruct patients to promptly discontinue QTERNMET XR and contact their healthcare provider if persistent severe abdominal pain occurs.

## **Heart Failure**

- Inform patients of the signs and symptoms of heart failure. Instruct patients to contact their healthcare provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet [*see* [WARNINGS AND PRECAUTIONS \(5.3\)](#)].

## **Hypotension**

- Inform patients that symptomatic hypotension may occur with QTERNMET XR and advise them to contact their healthcare provider if they experience such symptoms. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake [*see* [WARNINGS AND PRECAUTIONS \(5.4\)](#)].

## **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 QTERNMET XR and seek medical advice immediately [*see* [WARNINGS AND PRECAUTIONS \(5.5\)](#)].

## **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 QTERNMET XR use in those settings [*see* [WARNINGS AND PRECAUTIONS \(5.6\)](#)].

## **Serious Urinary Tract Infections**

- Inform patients of the potential for urinary tract infections, which may be serious. Inform them of the symptoms of urinary tract infections and advise them to seek medical advice if such symptoms occur [*see* [WARNINGS AND PRECAUTIONS \(5.7\)](#)].

### **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 QTERNMET 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 \(5.9\)](#)*].

### **Hypersensitivity Reactions**

- Inform patients that serious hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, and exfoliative skin conditions) have been reported with dapagliflozin and saxagliptin, components of QTERNMET XR. Symptoms of these allergic reactions include: rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing [*see [WARNINGS AND PRECAUTIONS \(5.10\)](#)*].
- Advise patients to immediately report any signs or symptoms suggesting allergic reaction, angioedema, or exfoliative skin conditions, and stop taking QTERNMET XR and seek medical advice promptly.

### **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 \(5.12\)](#)*].

### **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 \(5.12\)](#)*].

### **Bladder Cancer**

- Inform patients to promptly report any signs of macroscopic hematuria or other symptoms potentially related to bladder cancer [*see [WARNINGS AND PRECAUTIONS \(5.14\)](#)*].

### **Severe and Disabling Arthralgia**

- Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs [*see [WARNINGS AND PRECAUTIONS \(5.15\)](#)*].

### **Bullous Pemphigoid**

- Inform patients that bullous pemphigoid may occur with QTERNMET XR. Instruct patients to seek medical advice if blisters or erosions occur [see [WARNINGS AND PRECAUTIONS \(5.16\)](#)].

### **Pregnancy**

- Advise pregnant patients of the potential risk to a fetus with treatment with QTERNMET XR. Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant [see [USE IN SPECIFIC POPULATIONS \(8.1\)](#)].

### **Lactating Mothers**

- Advise patients that use of QTERNMET XR is not recommended while breastfeeding [see [USE IN SPECIFIC POPULATIONS \(8.2\)](#)].

### **Females and Males of Reproductive Potential**

- Inform female patients that treatment with metformin may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation [see [USE IN SPECIFIC POPULATIONS \(8.3\)](#)].

### **Laboratory Tests**

- Inform patients that due to its mechanism of action, patients taking QTERNMET XR will test positive for glucose in their urine.

### **Taking Dose**

- Instruct patients that QTERNMET 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.

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AstraZeneca Pharmaceuticals LP

Wilmington, DE 19850

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**MEDICATION GUIDE**  
**QTERNMET® XR (CUE-turnmet)**  
**(dapagliflozin, saxagliptin, and metformin hydrochloride)**  
**extended-release tablets, for oral use**

**What is the most important information I should know about QTERNMET XR?**

**Serious side effects can happen to people taking QTERNMET XR, including:**

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

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

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

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

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

The best way to keep from having a problem with lactic acidosis from metformin is to tell your healthcare provider if you have any of the problems in the list above. Your healthcare provider may decide to stop your QTERNMET XR for a while if you have any of these problems.

- **Inflammation of the pancreas (pancreatitis).** Saxagliptin, one of the medicines in QTERNMET XR, can cause inflammation of the pancreas, which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.

**Before you start taking QTERNMET XR,** tell your healthcare provider if you have ever had:

- inflammation of your pancreas (pancreatitis)
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels

It is not known if having these medical problems will make you more likely to get pancreatitis with QTERNMET XR.

Stop taking QTERNMET XR and contact your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

- **Heart failure.** Heart failure means your heart does not pump blood well enough.

**Before you start taking QTERNMET XR,** tell your healthcare provider if you have ever had heart failure or have problems with your kidneys.

Contact your healthcare provider right away if you have any of the following symptoms:

- increasing shortness of breath or trouble breathing, especially when you lie down
- swelling or fluid retention, especially in the feet, ankles, or legs
- an unusually fast increase in weight
- unusual tiredness

These may be symptoms of heart failure.

- **Dehydration.** QTERNMET 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

QTERNMET XR can have other serious side effects. See “**What are the possible side effects of QTERNMET XR?**”

#### **What is QTERNMET XR?**

QTERNMET XR is a prescription medicine that contains dapagliflozin, saxagliptin, and metformin hydrochloride. QTERNMET XR is used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.

- QTERNMET XR is not for people with type 1 diabetes.
- QTERNMET XR is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- QTERNMET XR is only for people currently taking metformin.
- It is not known if QTERNMET XR is safe and effective in children younger than 18 years of age.

#### **Who should not take QTERNMET XR?**

##### **Do not take QTERNMET XR if you:**

- are allergic to dapagliflozin, saxagliptin, metformin, or any of the ingredients in QTERNMET XR. See the end of this Medication Guide for a list of ingredients in QTERNMET XR.  
Symptoms of a **serious** allergic reaction to QTERNMET XR may include:
  - swelling of the face, lips, throat and other areas of your skin
  - difficulty with swallowing or breathing
  - skin rash, itching, flaking or peeling
  - raised red areas on your skin (hives)
 If you have any of these symptoms, stop taking QTERNMET XR and contact your healthcare provider or go to the nearest hospital emergency room right away.
- have moderate to severe kidney problems or are on dialysis.
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in your blood or urine).

##### **Before taking QTERNMET XR, tell your healthcare provider about all of your medical conditions, including if you:**

- have type 1 diabetes or have had diabetic ketoacidosis (increased ketones in your blood or urine).
- are going to have surgery.
- are eating less due to illness, surgery or a change in your diet.
- drink alcohol very often or drink a lot of alcohol in the short term (“binge” drinking).
- have kidney problems.
- have liver problems.
- have a history of urinary tract infections or problems urinating.
- have heart problems, including heart failure.
- have had swelling of the face, lips, tongue and throat (angioedema) when you used a medicine called a dipeptidyl peptidase-4 (DPP-4) inhibitor like saxagliptin, one of the medicines in QTERNMET XR. If you are not sure if you have taken this medicine, ask your healthcare provider.
- have or have had bladder cancer.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- are going to get injection of dye or contrast agents for an x-ray procedure. QTERNMET XR may need to be stopped for a short time. Talk to your healthcare provider about when you should stop QTERNMET XR and when you should start QTERNMET XR again. See “What is the most important information I should know about QTERNMET XR?”
- are pregnant or plan to become pregnant. QTERNMET XR may harm your unborn baby. If you are pregnant or plan to become pregnant, call your healthcare provider right away to talk about the best way to control your blood sugar.

- are a woman who has not gone through menopause (premenopausal) who does not have periods regularly or at all. QTERNMET XR can cause the release of an egg from an ovary in a woman (ovulation). This can increase your chance of getting pregnant.
- are breastfeeding or plan to breastfeed. It is not known if QTERNMET XR passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby if you are taking QTERNMET XR. Breastfeeding is not recommended while taking QTERNMET XR.

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

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

QTERNMET XR may affect the way other medicines work, and other medicines may affect how QTERNMET XR works. Contact your healthcare provider if you will be starting or stopping certain other types of medicines, such as antibiotics, or medicines that treat fungus or HIV/AIDS, because your dose of QTERNMET XR might need to be changed.

#### **How should I take QTERNMET XR?**

- Take QTERNMET XR exactly as your healthcare provider tells you to take it.
- Do not change your dose of QTERNMET XR without talking to your healthcare provider.
- Take QTERNMET by mouth 1 time each day in the morning with food.
- Swallow QTERNMET XR whole. Do not cut, crush or chew QTERNMET XR tablets.
- You may sometimes pass a soft mass in your stools (bowel movement) that looks like QTERNMET XR tablets.
- During periods of stress on the body, such as fever, trauma, infection or surgery, contact your healthcare provider right away as your medicine needs may change.
- Stay on your prescribed diet and exercise program while taking QTERNMET XR.
- Your healthcare provider may do certain blood tests before you start QTERNMET XR and during your treatment.
- Your healthcare provider should test your blood to measure how well your kidneys are working before and during your treatment with QTERNMET XR.
- Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your HbA1c.
- 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.
- QTERNMET XR will cause your urine to test positive for glucose.
- If you miss a daily dose of QTERNMET XR and it is more than 12 hours until your next dose, take the missed dose as soon as possible with food.
- If you miss a daily dose of QTERNMET XR and it is less than 12 hours until your next dose, skip the missed dose. Take the next dose at your regular time.
- If you take too much QTERNMET XR, call your healthcare provider, or go to the nearest hospital emergency room right away.

#### **What should I avoid while taking QTERNMET 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 QTERNMET XR?**

**QTERNMET XR may cause serious side effects, including:**

- See "**What is the most important information I should know about QTERNMET XR?**"
- **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 QTERNMET XR. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Ketoacidosis may lead to death. **Ketoacidosis can happen with dapagliflozin even if your blood sugar is less than 250 mg/dL. Stop taking QTERNMET XR and call your healthcare provider right away if you get any of the following symptoms:**
  - nausea
  - tiredness
  - vomiting
  - trouble breathing
  - stomach area (abdominal) pain



If you get any of these symptoms during treatment with QTERNMET 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 dapagliflozin. Talk to your healthcare provider right away if you:
  - reduce the amount of food or liquid you drink, for example if you are sick and cannot eat, or
  - you start to lose liquids from your body with 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. Tell your healthcare provider if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.
- **Low blood sugar (hypoglycemia).** If you take QTERNMET XR with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, this can increase your risk of getting low blood sugar. Tell your healthcare provider if you take other diabetes medicines. Signs and symptoms of low blood sugar may include:
  - shaking or feeling jittery
  - sweating
  - rapid heartbeat
  - change in vision
  - hunger
  - headache
  - drowsiness
  - weakness
  - change in mood
  - confusion
  - irritability
- **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 QTERNMET 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)
- **Serious allergic reaction.** QTERNMET XR may cause serious allergic reactions. Stop taking QTERNMET XR and get medical help right away if you develop any of the following symptoms of a serious allergic reaction including:
  - swelling of the face, lips, tongue, throat and other areas of your skin
  - difficulty with swallowing or breathing
  - skin rash, itching, flaking, or peeling
  - raised red patches on your skin (hives)
- **Low vitamin B<sub>12</sub> (vitamin B<sub>12</sub> deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B<sub>12</sub> in your blood, especially if you have had low vitamin B<sub>12</sub> levels before. Your healthcare provider may do blood tests to check your vitamin B<sub>12</sub> levels.
- **Vaginal yeast infection.** Women who take QTERNMET 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 QTERNMET 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 a 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 medicine 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 medicines. There were

too few cases to know if bladder cancer was related to dapagliflozin. You should not take QTERNMET 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

- **Joint pain.** Some people who take DPP-4 inhibitors like saxagliptin, may develop joint pain that can be severe. Call your healthcare provider right away if you have severe joint pain.
- **Skin reaction.** Some people who take DPP-4 inhibitors, one of the medicines in QTERNMET XR, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your healthcare provider right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your healthcare provider may tell you to stop taking QTERNMET XR.

**The most common side effects of QTERNMET XR include:**

- upper respiratory tract infection
- abnormal amounts of fats in the blood (dyslipidemia)
- urinary tract infection

These are not all of the possible side effects of QTERNMET XR.

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

**How should I store QTERNMET XR?**

Store QTERNMET XR at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep QTERNMET XR and all medicines out of the reach of children.**

**General information about the safe and effective use of QTERNMET XR.**

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

You can ask your pharmacist or healthcare provider for information about QTERNMET XR that is written for health professionals.

**What are the ingredients in QTERNMET XR?**

**Active ingredients:** dapagliflozin, saxagliptin, and metformin hydrochloride

**Inactive ingredients:** carboxymethyl cellulose sodium, crospovidone, hypromellose 2208, iron oxides, lactose anhydrous, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, macrogol/polyethylene glycol, silicon dioxide, talc, and titanium dioxide.

QTERNMET XR is a registered trademark of the AstraZeneca group of companies.

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For more information about QTERNMET XR, go to [www.QTERNMETXR.com](http://www.QTERNMETXR.com) or call 1-800-236-9933.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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