**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)**

**---------- RECENT MAJOR CHANGES ----------**

| | |
|---|---|
| Warnings and Precautions (5.5, 5.6) | 1/2020 |
| Warnings and Precautions (5.13, 5.14) | Removed 1/2020 |

**---------- 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 $m^2$), 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:* 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 $B_{12}$ deficiency*: Metformin may lower vitamin $B_{12}$ levels. Measure hematological parameters annually. (5.11, 6.1)
*Genital Mycotic Infections:* Monitor and treat if indicated. (5.12, 6.1)
*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. (5.13, 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. (5.14)
*Macrovascular Outcomes:* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with QTERNMET XR. (5.15)

**---------- 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.**

**---------- 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, 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: 1/2020**

**FULL PRESCRIBING INFORMATION: CONTENTS***



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

## FULL PRESCRIBING INFORMATION

**WARNING: LACTIC ACIDOSIS**

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL *[see WARNINGS AND PRECAUTIONS (5.1)]*.**
- **Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.**
- **Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information *[see DOSAGE AND ADMINISTRATION (2.2), CONTRAINDICATIONS (4), WARNINGS AND PRECAUTIONS (5.1), DRUG INTERACTIONS (7) and USE IN SPECIFIC POPULATIONS (8.6, 8.7)]*.**
- **If metformin-associated lactic acidosis is suspected, immediately discontinue 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 is10 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 $m^2$.

QTERNMET XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 $m^2$ *[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 anaphylactic reactions, 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 $m^2$), 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/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

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

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