

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 m²), 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 B₁₂ deficiency:** Metformin may lower vitamin B₁₂ 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.

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: 6/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LACTIC ACIDOSIS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of QTERNMET XR

2.2 Dosage

2.3 Patients with Renal Impairment

2.4 Use with Strong CYP3A4/5 Inhibitors

2.5 Discontinuation for Iodinated Contrast Imaging Procedures

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

5.2 Pancreatitis

5.3 Heart Failure

5.4 Hypotension

5.5 Ketoacidosis

5.6 Acute Kidney Injury and Impairment in Renal Function

5.7 Urosepsis and Pyelonephritis

5.8 Hypoglycemia with Concomitant Use of Insulin or Insulin Secretagogues

5.9 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

5.10 Hypersensitivity Reactions

5.11 Vitamin B12 Concentrations

5.12 Genital Mycotic Infections

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

5.14 Bladder Cancer

5.15 Severe and Disabling Arthralgia

5.16 Bullous Pemphigoid

5.17 Macrovascular Outcomes

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

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

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

14.3 Cardiovascular Safety Trial

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

- Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL [see [WARNINGS AND PRECAUTIONS \(5.1\)](#)].
- Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.
- Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information [see [DOSAGE AND ADMINISTRATION \(2.2\)](#), [CONTRAINDICATIONS \(4\)](#), [WARNINGS AND PRECAUTIONS \(5.1\)](#), [DRUG INTERACTIONS \(7\)](#) and [USE IN SPECIFIC POPULATIONS \(8.6, 8.7\)](#)].
- If metformin-associated lactic acidosis is suspected, immediately discontinue 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 m².

QTERNMET XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m² [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 m²), 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.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.