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

**QTERN® (dapagliflozin and saxagliptin) tablets, for oral use**
**Initial U.S. Approval: 2017**

---------- RECENT MAJOR CHANGES ----------
Warnings and Precautions (5.8) 10/2018

---------- **INDICATIONS AND USAGE** ----------
QTERN is a sodium-glucose cotransporter 2 (SGLT-2) inhibitor and a dipeptidyl peptidase-4 (DPP-4) inhibitor combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin. (1, 14)
Limitations of Use:
- Is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)
- Should only be used in patients who tolerate 10 mg dapagliflozin. (1)

---------- **DOSAGE AND ADMINISTRATION** ----------
The recommended dose of QTERN is a 10 mg dapagliflozin/5 mg saxagliptin tablet taken orally once daily in the morning with or without food. (2.1)
- Assess renal function before initiation of therapy and periodically thereafter. Do not initiate QTERN if eGFR is below 60 mL/min/1.73 $m^2$. (2.2)
- Discontinue QTERN if eGFR falls persistently below 60 mL/min/1.73 $m^2$. (2.2)
- Do not coadminister QTERN with strong cytochrome P450 3A4/5 inhibitors. (2.3, 7.1)
- Tablet should be swallowed whole and not be split or cut.

---------- **DOSAGE FORMS AND STRENGTHS** ----------
Tablet: 10 mg dapagliflozin/5 mg saxagliptin (3)

---------- **CONTRAINDICATIONS** ----------
QTERN is contraindicated in patients with:
- History of a serious hypersensitivity reaction to dapagliflozin or to saxagliptin, such as anaphylaxis, angioedema, or exfoliative skin conditions. (4, 5.8, 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)

---------- **WARNINGS AND PRECAUTIONS** ----------
*Pancreatitis:* If pancreatitis is suspected, promptly discontinue QTERN. (5.1, 6.2)
*Heart Failure:* Consider the risks and benefits of QTERN in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.2)
*Hypotension:* Before initiating QTERN, 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. (5.3, 6.1)
*Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue QTERN, evaluate and treat promptly. Before initiating QTERN, consider risk factors for ketoacidosis. Patients on QTERN may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.4, 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. (5.5, 6.2)
*Urosepsis and Pyelonephritis:* Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.6, 6.2)
*Hypoglycemia:* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating QTERN. (5.7, 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. (5.8)
*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 QTERN, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.9, 6.2)
*Genital Mycotic Infections:* Monitor and treat if indicated. (5.10, 6.1)
*Increased LDL-C:* Monitor and treat per standard of care. (5.11, 6.1)
*Bladder Cancer:* An imbalance in bladder cancers was observed in clinical studies with dapagliflozin. QTERN 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. (5.12)
*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 QTERN. (5.14)
*Macrovascular Outcomes:* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with QTERN. (5.15)

---------- **ADVERSE REACTIONS** ----------
Adverse reactions reported in ≥5% of subjects treated with 10 mg dapagliflozin and 5 mg saxagliptin 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 QTERN with strong cytochrome P450 3A4/5 inhibitors. (2.3, 7.1)

---------- **USE IN SPECIFIC POPULATIONS** ----------
*Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
*Lactation:* QTERN is not recommended when breastfeeding. (8.2)
*Geriatrics:* Higher incidence of adverse reactions related to volume depletion and reduced renal function. (5.3, 5.5, 8.5)
*Renal Impairment:* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.5, 6.1, 8.6)

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

**Revised: 10/2018**

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**FULL PRESCRIBING INFORMATION: CONTENTS***

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

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

QTERN (dapagliflozin and saxagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin *[see Clinical Studies (14)]*.

Limitations of Use

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

QTERN should only be used in patients who tolerate 10 mg dapagliflozin.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosage

In patients with volume depletion, correct this condition prior to initiation of QTERN *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5, 8.6)]*.

The recommended dose of QTERN is a 10 mg dapagliflozin/5 mg saxagliptin tablet taken orally once daily in the morning with or without food.

Do not split or cut QTERN tablets.

### 2.2 Patients with Renal Impairment

Assessment of renal function is recommended prior to initiation of QTERN therapy and periodically thereafter.

Do not initiate QTERN in patients with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 $m^2$.

Discontinue QTERN if eGFR falls persistently below 60 mL/min/1.73 $m^2$ *[see Warnings and Precautions (5.5)* and *Use in Specific Populations (8.6)]*.

QTERN is contraindicated in patients with an eGFR less than 45 mL/min/1.73 $m^2$ *[see Contraindications (4)]*.

### 2.3 Use with Strong CYP3A4/5 Inhibitors

Do not coadminister QTERN with strong cytochrome P450 3A4/5 inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) *[see Drug Interactions (7.1)]*.

## 3 DOSAGE FORMS AND STRENGTHS

QTERN tablets containing 10 mg dapagliflozin and 5 mg saxagliptin are light brown to brown, biconvex, round, film-coated, with “1122” printed on both sides of the tablet, in blue ink.

## 4 CONTRAINDICATIONS

QTERN is contraindicated in patients with:

- History of a serious hypersensitivity reaction to dapagliflozin or to saxagliptin , including anaphylaxis, angioedema or exfoliative skin conditions *[see Warnings and Precautions (5.8)* 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)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 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 QTERN, observe patients for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue QTERN 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 QTERN.

### 5.2 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 QTERN 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 QTERN.

### 5.3 Hypotension

Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating QTERN *[see Adverse Reactions (6.1)]* particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 $m^2$), elderly patients, or patients on loop diuretics. Before initiating QTERN volume status should be assessed and corrected. Do not initiate QTERN in patients with an eGFR <60 mL/min/1.73 $m^2$. Monitor for signs and symptoms of hypotension after initiating therapy.

### 5.4 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 (SGLT-2) inhibitors, including dapagliflozin. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. QTERN is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

Patients treated with QTERN 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 QTERN may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, QTERN 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 QTERN, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction and

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