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

INDICATIONS AND USAGE

• Assess renal function before initiation of therapy and periodically thereafter. (2.1)
• Take QTERN orally, once daily in the morning with or without food. (2.2)
• For patients not already taking dapagliflozin, the recommended starting dose of QTERN is a 5 mg dapagliflozin/5 mg saxagliptin tablet once daily. (2.2)
• In patients tolerating 5 mg dapagliflozin and 5 mg saxagliptin once daily who require additional glycemic control, the QTERN dose can be increased to 10 mg dapagliflozin/10 mg saxagliptin tablet once daily. (2.2)
• Do not coadminister QTERN with strong cytochrome P450 3A4/5 inhibitors. (2.4, 7)

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 m²), 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: 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)

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. (5.11, 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. (5.12)

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with QTERN. (5.13)

ADVERSE REACTIONS

Adverse reactions reported in ≥5% of subjects treated with dapagliflozin and 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)

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. (5.3, 5.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 1/2020

DRUG INFORMATION

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

9 PATIENT COUNSELING INFORMATION

17 MEDICATION GUIDE

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2 DOSAGE AND ADMINISTRATION

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

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been identified 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. 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 serious diabetic ketoacidosis 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 infection or surgery, acute febrile illness, reduced concomitant insulin, intercurrent disorders (e.g., urine infection), 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 alcohol abuse.

For patients who undergo elective surgery, consider temporarily discontinuing QTERN for at least 3 days prior to surgery [see Clinical Pharmacology (12.2, 12.3)].

Consider monitoring for ketoacidosis and temporarily discontinuing QTERN in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery) [see ADVERSE REACTIONS (6.1)]. Ensure risk factors for ketoacidosis are resolved prior to restarting QTERN.

Educate patients and their caregivers about the signs and symptoms of ketoacidosis and the importance of monitoring blood glucose levels. Patients and their caregivers should be instructed to immediately report such symptoms [see ADVERSE REACTIONS (6.1)]. If ketoacidosis is suspected, QTERN should be discontinued and treatment with insulin should be initiated immediately with appropriate electrolyte and fluid replacement.

5.5 Acute Kidney Injury

Dapagliflozin causes intravascular volume contraction [see WARNINGS AND PRECAUTIONS (5.3, 5.5)], and can cause acute kidney injury. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving dapagliflozin.

Increases in serum creatinine and decreases in estimated GFR may also be observed with initiation of QTERN. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Before initiating QTERN, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic or acute heart failure, and concomitant medications (diuretics, ACE inhibitors, ARBs, and NSAIDs). Consider temporarily discontinuing QTERN in the setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue QTERN promptly and institute treatment.

Renal function should be evaluated prior to initiation of QTERN and monitored periodically thereafter. QTERN is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m² [see DOSAGE AND ADMINISTRATION (2.3), CONTRAINDICATIONS (4) and USE IN SPECIFIC POPULATIONS (8.6)].

5.6 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)].

5.7 Hypoglycemia with Concomitant Use of Insulin or Insulin Secretagogues

Insulin and insulin secretagogues, such as sulfonylureas, are known to cause hypoglycemia. Both dapagliflozin and saxagliptin can individually increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. 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 QTERN [see ADVERSE REACTIONS (6.1)].

5.8 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 both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with QTERN 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 QTERN, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.9 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with saxagliptin. These reactions include anaphylactic reactions, 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 QTERN, 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.

5.10 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.

5.11 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)].

5.12 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 QTERN. If bullous pemphigoid is suspected, QTERN should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

5.13 Macrovacular Outcomes

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

6 ADVERSE REACTIONS

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

- Pancreatitis [see WARNINGS AND PRECAUTIONS (5.1)]
- Heart Failure [see WARNINGS AND PRECAUTIONS (5.2)]
- Hypotension [see WARNINGS AND PRECAUTIONS (5.3)]
- Hyperkalemia [see WARNINGS AND PRECAUTIONS (5.4)]
- Acute Kidney Injury [see WARNINGS AND PRECAUTIONS (5.5)]
- Urosepsis and Pyelonephritis [see WARNINGS AND PRECAUTIONS (5.6)]
- Hypersensitivity Reactions [see WARNINGS AND PRECAUTIONS (5.8)]
- Genital Mycotic Infections [see WARNINGS AND PRECAUTIONS (5.10)]
- Severe and Disabling Arthralgia [see WARNINGS AND PRECAUTIONS (5.11)]
- Bullous Pemphigoid [see WARNINGS AND PRECAUTIONS (5.12)]

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, and 336 patients in 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 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 baseline HbA1c of 8.4%. The mean eGFR at baseline was 94.4 mL/min/1.73 m².

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of dapagliflozin and saxagliptin. 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.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Preferred Term*</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection*</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection*</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia*</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Genital infection*</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.4</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Hypoglycemia

In the pooled analysis, the incidences of hypoglycemia (defined as a blood glucose ≤54 mg/dL, regardless of the presence or absence of symptoms) and severe hypoglycemia (event requiring assistance due to neuroglycopenia, characterized by altered mental and/or physical status) was 1% and 0.2%, respectively.
Dapagliflozin
- Ketoacidosis
- Acute Kidney Injury
- 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
- Rhabdomyolysis

7 DRUG INTERACTIONS

Table 2: Clinically Relevant Interactions Affecting Drugs Coadministered with QTERN

<table>
<thead>
<tr>
<th>Strong Inhibitors of CYP3A4/5 Enzymes</th>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>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, saquinavir, and telithromycin).</td>
<td>Do not coadminister QTERN with strong cytochrome P450 3A4/5 inhibitors [see DOSAGE AND ADMINISTRATION (2.3) and CLINICAL PHARMACOLOGY (12.3)].</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Positive Urine Glucose Test</th>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.</td>
<td>Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interference with 1.5-anhydroglucitol (1,5-AG) Assay</th>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.</td>
<td>Monitoring glycemic control with 1.5-AG assay is not recommended. Use alternative methods to monitor glycemic control.</td>
<td></td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects from dapagliflozin, QTERN is not recommended during the second and third trimesters of pregnancy. The limited available data with QTERN or its components (dapagliflozin and saxagliptin) in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. 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 QTERN) 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).

8.5 Geriatric Use

Because elderly patients are more likely to have decreased renal function, care should be taken when using QTERN in the elderly based on renal function [see DOSAGE AND ADMINISTRATION (2.2)].

Dapagliflozin

A total of 1424 (24%) of the 5936 dapagliflozin-treated patients were 65 years and older and 153 (2%) were 65 years and older in a pool of 21 double-blind, controlled clinical studies assessing the efficacy of dapagliflozin in improving glycemic control. 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 of hypotension [see WARNINGS AND PRECAUTIONS (5.3)].

Saxagliptin

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

8.6 Renal Impairment

QTERN is contraindicated in patients with moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m²), ESRD, or on dialysis [see DOSAGE AND ADMINISTRATION (2.3), CONTRAINDICATIONS (4) and WARNINGS AND PRECAUTIONS (5.3)].

Dapagliflozin

Dapagliflozin was evaluated in two glycemic control studies that included patients with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m²), and an eGFR of 30 to less than 60 mL/min/1.73 m². The safety profile of dapagliflozin in the study of patients with an eGFR of 45 to less than 60 mL/min/1.73 m² 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.

Data

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 ≥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.

8.7 Hepatic Impairment

QTERN may be used in patients with hepatic impairment. However, the benefit-risk for the use of QTERN in patients with severe hepatic impairment should be individually assessed since safety and efficacy have not been studied in this population [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).

11 DESCRIPTION
QTERN tablets for oral use contain dapagliflozin and saxagliptin.

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_{18}H_{25}N_{3}O_{2}. The molecular weight is 333.43. The structural formula is:

![Dapagliflozin Structural Formula](image)

Saxagliptin is an active inhibitor of the dipeptidyl-peptidase-4 (DPP-4) enzyme. It is isolated in the monohydrate form chemically known as (1S,3S,5S)-2-[(2S)-2-amino-2-[(3-hydroxytricyclo [3.3.1.1] dec-1-yl)acetyl]-2-azacyclo[3.1.0]hexane-3-carbonitrole, monohydrate or (1S,3S,5S)-2-[(2S)-2-amino-2-[(3-hydroxy-1-adamantan-1-yl)acetyl]-2-azacyclo[3.1.0]hexane-3-carbonitrole hydrate. The empirical formula is C_{18}H_{25}N_{3}O_{2}. The molecular weight is 355.43. The structural formula is:

![Saxagliptin Structural Formula](image)

Saxagliptin is available as film-coated tablets of two strengths:

• 5 mg dapagliflozin/5 mg saxagliptin. Each tablet contains 5 mg dapagliflozin (equivalent to 6.15 mg dapagliflozin propanediol) and 5 mg saxagliptin (exists in the form of HCl salt).

• 10 mg dapagliflozin/5 mg saxagliptin. Each tablet contains 10 mg dapagliflozin (equivalent to 12.3 mg dapagliflozin propanediol) and 5 mg saxagliptin (exists in the form of HCl salt).

Each tablet also contains the following inactive ingredients: anhydrous lactose, crosscarmellose sodium, iron oxides, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, 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
QTERN contains: dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and saxagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor.

Dapagliflozin
Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the major 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.

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)]. After discontinuation of dapagliflozin, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days from discontinuation for the 10 mg dose.

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

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 dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs T_{max} by approximately 1 hour but 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 2 hours for saxagliptin and 4 hours for its active metabolite. Administration with a high-fat meal resulted in an increase in T_{max} of saxagliptin by approximately 20 minutes as compared to fasted conditions. There was a 27% increase in the AUC of saxagliptin when given with a meal as compared to fasted conditions.

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.

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 [14C] 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 DPP4 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)].

Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-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 (t1/2) 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 [14C]-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 (t1/2) for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.

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 saxagliptin and dapagliflozin.

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 with 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 Cmax or AUC of saxagliptin or its metabolite. In subjects with moderate renal impairment (eGFR 30 to less than 45 mL/min/1.73 m²), severe renal impairment (eGFR 15 to less than 30 mL/min/1.73 m²) 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. OTERIN is contraindicated in patients with an eGFR <35 mL/min/1.73 m².

Hepatic Impairment

Dapagliflozin

In subjects with mild and moderate hepatic impairment (Child-Pugh classes A and B), mean Cmax and AUC of dapagliflozin were up to 12% and 38% 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 Cmax and AUC of dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls [see USE IN SPECIFIC POPULATIONS (8.7)].

Saxagliptin

In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean Cmax 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 Cmax 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.

Pediatric

Pharmacokinetics of OTERIN in the pediatric population has not been studied.
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.

Effects of Other Drugs on Saxagliptin and its Active Metabolite, 5-hydroxy Saxagliptin

Table 6: Effect of Saxagliptin on Systemic Exposures of Coadministered Drugs (cont’d)

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dosage of Coadministered Drug*</th>
<th>Dosage of Saxagliptin*</th>
<th>Change in AUC†</th>
<th>Change in Cmax†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1000 mg</td>
<td>100 mg</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>10 mg</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>45 mg for 10 days</td>
<td>10 mg for 5 days</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>10 mg single dose</td>
<td>5 mg single dose</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40 mg for 8 days</td>
<td>10 mg for 4 days</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>360 mg for 9 days</td>
<td>10 mg</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Rifampin†</td>
<td>600 mg for 6 days</td>
<td>5 mg</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>40 mg for 5 days</td>
<td>10 mg</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Aluminum hydroxide + magnesium hydroxide + simethicone</td>
<td>10 mg</td>
<td>saxagliptin</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Famotidine</td>
<td>40 mg</td>
<td>10 mg</td>
<td>13%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Saxagliptin coadministered with strong CYP3A4/5 inhibitors [see DRUG INTERACTIONS (7) and DOSAGE AND ADMINISTRATION (2.3)].

Ketoconazole

Results include all subjects.

Percent change (with/without coadministered drug and no change=0%); 1 and 4 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 exclude one subject.

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 6: Effect of Saxagliptin on Systemic Exposures of Coadministered Drugs

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<tr>
<th>Coadministered Drug</th>
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<td>Metformin</td>
<td>1000 mg</td>
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<td>19%</td>
</tr>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>10 mg</td>
<td>16%</td>
<td>11%</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>45 mg for 10 days</td>
<td>10 mg for 5 days</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>0.25 mg q8h first day followed by q12h second day followed by QD for 5 days</td>
<td>10 mg for 7 days</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40 mg for 8 days</td>
<td>10 mg for 4 days</td>
<td>14%</td>
<td>11%</td>
</tr>
</tbody>
</table>

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

* Percent change (with/without coadministered drug and no change=0%); 1 and 4 indicate the exposure increase and decrease, respectively.

† Results exclude one subject.

‡ The plasma dipeptidyl peptidase-4 (DPP-4) activity inhibition over a 24-hour dose interval was not affected by rifampin.

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† Results exclude one subject.

‡ The plasma dipeptidyl peptidase-4 (DPP-4) activity inhibition over a 24-hour dose interval was not affected by rifampin.

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

* Percent change (with/without coadministered drug and no change=0%); 1 and 4 indicate the exposure increase and decrease, respectively.

† Results exclude one subject.

‡ The plasma dipeptidyl peptidase-4 (DPP-4) activity inhibition over a 24-hour dose interval was not affected by rifampin.
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 in combination 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 ≥7.5% and ≤10%. Patients were on a stable dose of metformin (≥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 0.5 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 7).

Table 7: HbA1c Results at Week 24 with the Combination of 5 mg Dapagliflozin and 5 mg Saxagliptin plus Metformin*

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>5 mg Dapagliflozin + 5 mg Saxagliptin + Metformin</th>
<th>5 mg Dapagliflozin + Metformin</th>
<th>5 mg Saxagliptin + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>290</td>
<td>289</td>
<td>291</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.1</td>
<td>8.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean) (95% CI)</td>
<td>-1.02 (-1.15, -0.89)</td>
<td>-0.62 (-0.73, -0.51)</td>
<td>-0.69 (-0.80, -0.59)</td>
</tr>
<tr>
<td>Difference from saxagliptin + metformin (adjusted mean) (95% CI)</td>
<td>-0.40 (-0.55, -0.24)</td>
<td>-0.32 (-0.48, -0.17)</td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving HbA1c &lt;7%</td>
<td>42.8</td>
<td>21.8</td>
<td>28.5</td>
</tr>
</tbody>
</table>

* 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 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, -1.1]).

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, -1.1]).

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 >8% and ≤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 8).

Table 8: HbA1c Results at Week 24 with the Combination of 10 mg Dapagliflozin and 5 mg Saxagliptin plus Metformin*

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>10 mg Dapagliflozin + 5 mg Saxagliptin + Metformin</th>
<th>10 mg Dapagliflozin + Metformin</th>
<th>5 mg Saxagliptin + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>179</td>
<td>179</td>
<td>176</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.9</td>
<td>8.9</td>
<td>9.0</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean) (95% CI)</td>
<td>-1.49 (-1.64, -1.34)</td>
<td>-1.23 (-1.38, -1.08)</td>
<td>-1.00 (-1.15, -0.85)</td>
</tr>
<tr>
<td>Difference from dapagliflozin + metformin (adjusted mean) (95% CI)</td>
<td>-0.28 (-0.47, -0.05)</td>
<td>-0.49 (-0.70, -0.27)</td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving HbA1c &lt;7%</td>
<td>40.2</td>
<td>21.1</td>
<td>16.5</td>
</tr>
</tbody>
</table>

* 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 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).

There were at least 40 years of age, had HbA1c ≥6.5%, and multiple risk factors (21% of randomized subjects for cardiovascular disease [age ≥5 years for men and ≥6 years for women], 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 73%, 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 30 to ≤50 mL/min/1.73 m2) to severe (eGFR <30 mL/min/1.73 m2) renal impairment, and 13% had a prior history of heart failure. QTNR is contraindicated in patients with an eGFR <45 mL/min/1.73 m2.

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% CI: (0.89, 1.12). The upper bound of this confidence interval, 1.12, excluded a risk margin larger than 1.3.

The number of randomized subjects who took at least one dose of double-blind study medication and had a baseline value for HbA1c: 4,331.

p-value <0.0001.

There were 56% (n=284) of randomized subjects in the saxagliptin arm who had a change from baseline HbA1c data missing at Week 24.

The group treated with add-on saxagliptin had statistically significant greater reductions in HbA1c from baseline versus the group treated with placebo (see Table 9).

Table 9: HbA1c Change from Baseline at Week 24 in a Placebo-Controlled Trial of Saxagliptin as Add-on to Dapagliflozin and Metformin*

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>5 mg Saxagliptin (N=153)†</th>
<th>Placebo (N=162)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mean)</td>
<td>8.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean) (95% CI)</td>
<td>-0.5 (-0.6, -0.4)</td>
<td>-0.2 (-0.3, -0.1)</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean) (95% Confidence Interval)</td>
<td>-0.4† (-0.5, -0.2)</td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving HbA1c &lt;7%</td>
<td>35.3</td>
<td>23.1</td>
</tr>
</tbody>
</table>

* There were 56% (n=108) of randomized subjects in the saxagliptin arm and 31% (n=51) in the placebo arm for whom change from baseline HbA1c data was missing at Week 24. Of the subjects who discontinued study medication early (11% (1 of 11) in the saxagliptin arm and 16.7% (1 of 6) in the placebo arm), HbA1c was measured at Week 24.

† N is the number of randomized and treated patients.

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.

Least squares means adjusted for baseline value.

p-value <0.0001.
16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied
QTERN® (dapagliflozin and saxagliptin) tablets for oral use are available in packages as listed:

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Film-Coated Tablet Color / Shape</th>
<th>Tablet Markings</th>
<th>Pack Size</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>Light purple, brown, biconvex, round</td>
<td>&quot;1120&quot; printed on both sides, in blue ink</td>
<td>Bottles of 30</td>
<td>0310-6770-30</td>
</tr>
<tr>
<td>saxagliptin</td>
<td></td>
<td></td>
<td>Bottles of 90</td>
<td>0310-6770-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bottles of 500</td>
<td>0310-6770-50</td>
</tr>
<tr>
<td>10 mg</td>
<td>Light brown to reddish purple, biconvex, round</td>
<td>&quot;1122&quot; printed on both sides, in blue ink</td>
<td>Bottles of 30</td>
<td>0310-6780-30</td>
</tr>
<tr>
<td>saxagliptin</td>
<td></td>
<td></td>
<td>Bottles of 90</td>
<td>0310-6780-90</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Bottles of 500</td>
<td>0310-6780-50</td>
</tr>
</tbody>
</table>

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).

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.
- Instruct patients to promptly discontinue QTERN and contact their healthcare provider if persistent severe abdominal pain occurs [see WARNINGS AND PRECAUTIONS (5.1)].

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 (5.2)].

Hypotension
- Inform patients that symptomatic hypotension may occur with QTERN 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 (5.3)].

Ketoacidosis
- Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of dapagliflozin, sometimes associated with illness or surgery among other risk factors. 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 QTERN and seek medical attention immediately [see WARNINGS AND PRECAUTIONS (5.4)].

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 QTERN use in those settings [see WARNINGS AND PRECAUTIONS (5.5)].

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 (5.6)].

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 QTERN. 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 (5.8)].

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 QTERN. 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.
- Advise patients to immediately report any signs or symptoms suggesting allergic reaction, angioedema or exfoliative skin conditions, and stop taking QTERN and seek medical advice promptly [see WARNINGS AND PRECAUTIONS (5.9)].

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 (5.10)].

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 (5.11)].

Bullous Pemphigoid
- Inform patients that bullous pemphigoid may occur with QTERN. Instruct patients to seek medical advice if blisters or erosions occur [see WARNINGS AND PRECAUTIONS (5.12)].

Pregnancy
- Advise pregnant patients of the potential risk to a fetus with treatment with QTERN. 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 QTERN is not recommended while breastfeeding [see USE IN SPECIFIC POPULATIONS (8.2)].

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

Administration
- Instruct patients that QTERN 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.

Missing Dose
- If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of QTERN at the same time.

Distributed by: AstraZeneca Pharmaceuticals LP
Willmington, DE 19850

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01/20 US-36669 1/20
What is the most important information I should know about QTERN?

Serious side effects can happen to people taking QTERN, including:

- **Inflammation of the pancreas (pancreatitis).** Saxagliptin, one of the medicines in QTERN, 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 QTERN,** 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 these medical problems will make you more likely to get pancreatitis with QTERN. Stop taking QTERN 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 QTERN,** tell your healthcare provider if you have ever had heart failure or 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.** QTERN 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

Who should not take QTERN?

Do not take QTERN if you:

- are allergic to dapagliflozin, saxagliptin, or any of the ingredients in QTERN. See the end of this Medication Guide for a list of ingredients in QTERN.
- are eating less, or there is 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 a history of swelling of the face, lips, tongue and throat (angioedema) when you have taken a dipeptidyl peptidase 4 (DPP-4) inhibitor like saxagliptin one of the medicines in QTERN. If you are not sure if you have taken this medicine before, ask your healthcare provider.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- are pregnant or plan to become pregnant. QTERN may harm your unborn baby. If you are pregnant or plan to become pregnant, talk to your doctor about the best way to control your blood sugar.
- are breastfeeding or plan to breastfeed. It is not known if QTERN passes into your breast milk. Talk with your healthcare provider about the best way to control your blood sugar.
- are having surgery about when to stop taking QTERN and when to start it again.
- are eating less, or there is a change in your diet.
- drink alcohol very often or drink a lot of alcohol in the short term (“binge” drinking).

Before taking QTERN, 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).
- have had a history of swelling of the face, lips, tongue and throat (angioedema) when you have taken a dipeptidyl peptidase 4 (DPP-4) inhibitor like saxagliptin one of the medicines in QTERN. If you are not sure if you have taken this medicine before, ask your healthcare provider.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- are pregnant or plan to become pregnant. QTERN may harm your unborn baby. If you are pregnant or plan to become pregnant, talk to your healthcare provider about the best way to control your blood sugar.
- are breastfeeding or plan to breastfeed. It is not known if QTERN passes into your breast milk. Talk with your healthcare provider about the best way to control your blood sugar.
- are having surgery about when to stop taking QTERN and when to start it again.

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.

QTERN may affect the way other medicines work, and other medicines may affect how QTERN 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 QTERN might need to be changed.
**How should I take QTERN?**
- Take QTERN exactly as your healthcare provider tells you to take it.
- Do not change your dose of QTERN without talking to your healthcare provider.
- Take QTERN by mouth 1 time each day in the morning with or without food.
- Swallow QTERN whole. Do not cut, crush or chew QTERN tablets.
- During periods of stress on the body, such as fever, trauma, infection, or surgery, contact your healthcare provider right away as your medicine may need to be changed.
- Stay on your prescribed diet and exercise program while taking QTERN.
- Your healthcare provider may do certain blood tests before you start QTERN 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 QTERN.
- Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your HbA1c.
- QTERN will cause your urine to test positive for glucose.
- 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.
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the medicine at the next regularly scheduled time. Do not take 2 doses of QTERN at the same time unless your healthcare provider tells you to do so. Talk to your healthcare provider if you have questions about a missed dose.
- If you take too much QTERN, call your healthcare provider, or go to the nearest hospital emergency room right away.

**What are the possible side effects of QTERN?**

**QTERN may cause serious side effects, including:**
- See “What is the most important information I should know about QTERN?”
- **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis has happened in people who have type 1 or type 2 diabetes, during treatment with dapagliflozin, one of the medicines in QTERN. Ketoacidosis has also happened in people with diabetes who were sick or who had surgery during treatment with dapagliflozin. 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 QTERN and call your healthcare provider right away if you get any of the following symptoms:
  - nausea
  - trouble breathing
  - tiredness
  - stomach area (abdominal) pain
  - vomiting
If you get any of these symptoms during treatment with QTERN, 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 QTERN 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 QTERN. 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.** QTERN may cause serious allergic reactions. Stop taking QTERN 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, and 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)
• **Vaginal yeast infection.** Women who take QTERN 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 QTERN 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 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.

• **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 like saxagliptin, one of the medicines in QTERN, 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 QTERN.

The most common side effects of QTERN include:
- upper respiratory tract infection
- urinary tract infection
- abnormal amounts of fats in the blood (dyslipidemia)

These are not all of the possible side effects of QTERN. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store QTERN?
Store QTERN at room temperature between 68°F to 77°F (20°C to 25°C).

Keep QTERN and all medicines out of the reach of children.

General information about the safe and effective use of QTERN.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use QTERN for a condition for which it was not prescribed. Do not give QTERN 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 QTERN that is written for health professionals.

What are the ingredients in QTERN?
**Active ingredients:** dapagliflozin and saxagliptin
**Inactive ingredients:** anhydrous lactose, croscarmellose sodium, iron oxides, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, silicon dioxide, talc, and titanium dioxide.

QTERN is a registered trademark of the AstraZeneca group of companies.
Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

For more information about QTERN, go to www.QTERN.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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