PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrQTERN®

saxagliptin and dapagliflozin tablets

(as saxagliptin hydrochloride and dapagliflozin propanediol monohydrate)

5 mg/5 mg and 5 mg/10 mg

ATC Code: A10BD21

Combinations of oral blood glucose lowering drugs

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PART I: HEALTH PROFESSIONAL INFORMATION

Note: for additional information on saxagliptin and dapagliflozin, consult the individual Product Monographs.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablet / 5 mg/ 5 mg and 5 mg / 10 mg	Lactose *For a complete listing see Dosage Forms, Composition and Packaging section*.

INDICATIONS AND CLINICAL USE

QTERN (saxagliptin/dapagliflozin) is indicated for use in combination with metformin as an adjunct to diet and exercise to achieve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are:

- inadequately controlled on metformin and saxagliptin alone, or
- already controlled with metformin, saxagliptin and dapagliflozin, as individual components.

(see CLINICAL TRIALS).

Geriatrics (≥65 years of age): QTERN is not recommended in patients aged 75 years and older due to very limited experience. Use QTERN with caution in patients aged 65 and older. Experience with QTERN in patients aged 65 years and older is limited. Elderly patients treated with dapagliflozin had more adverse reactions related to volume depletion and renal impairment or failure, compared to patients treated with placebo (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Pediatrics (<18 years of age): QTERN should not be used in pediatric patients. Safety and effectiveness of QTERN or its monocomponents have not been established in this patient population.

CONTRAINDICATIONS

QTERN is contraindicated in patients with:

- a history of hypersensitivity reaction to the active substances, any of the excipients, or to any dipepidyl peptidase 4 (DPP4) or sodium-glucose co-transporter 2 (SGLT2) inhibitor. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- moderate to severe renal impairment, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, end-stage renal disease [ESRD] or on dialysis.
- diabetic ketoacidosis, diabetic coma/precoma or Type I diabetes mellitus. These conditions should be treated with insulin.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Diabetic Ketoacidosis

- QTERN is contraindicated in patients with diabetic ketoacidosis (DKA), diabetic coma/precoma or Type I diabetes mellitus. QTERN should not be used in patients with a history of DKA.
- Clinical trial and post-market cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus (T2DM) treated with dapagliflozin and other SGLT2 inhibitors. A number of these cases have been atypical with blood glucose values below 13.9 mmol/L (250 mg/dL) (see ADVERSE REACTIONS, Description of Selected Adverse Reactions). Some cases of DKA have been fatal.
- Patients should be assessed for DKA immediately if non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst and unusual fatigue or sleepiness occur, regardless of blood glucose level. If DKA is suspected or diagnosed, QTERN should be **discontinued immediately**.

Carcinogenesis and Mutagenesis

Bladder Cancer: QTERN should not be used in patients with active bladder cancer and should be used with caution in patients with a history of bladder cancer.

An imbalance in bladder cancers was observed in clinical trials with dapagliflozin. There are insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumours (see ADVERSE REACTIONS, Description of Selected Adverse Reactions).

Use in patients treated with pioglitazone: The relationship between dapagliflozin, pioglitazone and bladder cancer is uncertain. Therefore, QTERN is not indicated for use in patients treated with pioglitazone.

Cardiovascular

Patients with Congestive Heart Failure: Use QTERN with caution in patients with a history of congestive heart failure, especially those who also have renal impairment and/or history of myocardial infarction (MI). During therapy with QTERN, patients should be observed for signs and symptoms of heart failure. Patients should be advised of characteristic symptoms of heart failure, and to immediately report such symptoms. If heart failure develops, discontinue QTERN and manage according to current standards of care.

In a post-market placebo-controlled cardiovascular outcomes trial (SAVOR), hospitalization for heart failure occurred at a greater rate in the saxagliptin group (3.5%) compared to the placebo group (2.8%) [HR =1.27; 95% confidence interval 1.07, 1.51]. In the SAVOR trial, 2105 (12.8%) patients had a history of congestive heart failure, of whom 1056 were randomized to saxagliptin treatment (see ADVERSE REACTIONS, Description of Selected Adverse Reactions).

Use in Patients at Risk for Volume Depletion, Hypotension and/or Electrolyte Imbalances:

QTERN should not be used in patients who are volume depleted.

Dapagliflozin (a component of QTERN) causes diuresis that may be associated with decreases in blood pressure, which may be more pronounced in patients with high blood glucose concentrations.

Patients most susceptible to adverse reactions related to reduced intravascular volume (e.g., postural dizziness, orthostatic hypotension, hypotension or renal failure) include patients with renal impairment, patients with known cardiovascular disease, patients on antihypertensive therapy (particularly on loop diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs])), elderly patients, patients with low systolic blood pressure, or in case of intercurrent conditions that may lead to volume depletion (such as gastrointestinal illness).

Careful monitoring of volume status is recommended. Temporary interruption of QTERN is recommended for patients who develop volume depletion until the depletion is corrected (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and ADVERSE REACTIONS, Description of Selected Adverse Reactions).

Endocrine and Metabolism

Diabetic Ketoacidosis: QTERN is contraindicated in patients with diabetic ketoacidosis (DKA), diabetic coma/precoma or Type I diabetes mellitus (see CONTRAINDICATIONS).

QTERN should not be used in patients with a history of DKA. The diagnosis of T2DM should therefore be confirmed before initiating QTERN.

Clinical trial and post-market cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with T2DM treated with dapagliflozin and other SGLT2 inhibitors. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values below 13.9 mmol/L (250 mg/dL) (see ADVERSE REACTIONS, Description of Selected Adverse Reactions). Some cases of DKA have been fatal.

DKA must be considered in the event of non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst, and unusual fatigue or sleepiness. **If DKA is suspected, regardless of blood glucose level, patients should discontinue QTERN treatment and be assessed for DKA immediately.**

Interruption of treatment with QTERN should be considered in T2DM patients who are hospitalized for major surgical procedures, serious infections or acute serious medical illness.

Conditions that can precipitate DKA while taking QTERN include a very low carbohydrate diet (as the combination may further increase ketone body production), dehydration, high alcohol consumption and a low beta-cell function reserve. These patients should be monitored closely.

Hypoglycemia: QTERN has not been studied and is not indicated in combination with insulin and insulin secretagogues, such as sulfonylureas. Both saxagliptin and dapagliflozin can individually increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue (see ADVERSE REACTIONS, Description of Selected Adverse Reactions).

Loss of control of blood glucose: When a patient stabilized on QTERN is exposed to stress such as fever, trauma, infection, or surgery, a loss of control of blood glucose may occur. At such times, it may be necessary to temporarily discontinue QTERN and administer insulin.

Use with potent CYP 3A4 inducers: Glycemic control should be carefully assessed when QTERN is used concomitantly with a potent CYP3A4 inducer. Using CYP3A4 inducers like carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampin may reduce the glycemic lowering effect of saxagliptin (see DRUG INTERACTIONS).

Increases in Low-Density Lipoprotein (LDL-C): LDL-C levels should be monitored after initiating QTERN. Dose-related increases in LDL-C are seen with dapagliflozin treatment (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

Gastrointestinal

Lactose: QTERN tablets contain anhydrous lactose. Patients with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this product.

Genitourinary

Genital Mycotic Infections: Patients, particularly those with a history of genital mycotic infections, should be advised that dapagliflozin increases the risk of genital mycotic infections (see ADVERSE REACTIONS).

Urinary tract infections (including urosepsis and pyelonephritis): Treatment with QTERN increases the risk for urinary tract infections. In clinical trials with QTERN, a serious case of pyelonephritis was reported. There have been post-marketing reports of serious urinary tract infections requiring hospitalization, including pyelonephritis and urosepsis in patients treated with dapagliflozin (see ADVERSE REACTIONS).

Hematologic

Elevated Hemoglobin and Hematocrit: Use QTERN with caution in patients with an elevated hematocrit. Mean hemoglobin and hematocrit increased in patients administered QTERN, as did the frequency of dapagliflozin-treated patients with abnormally elevated values for hemoglobin/hematocrit (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

Hepatic/Biliary/Pancreatic

Hepatic: The use of QTERN in patients with moderate to severe hepatic impairment is not recommended. There is no QTERN experience in patients with hepatic impairment. Elevations in hepatic transaminases have been reported in dapagliflozin-treated patients in clinical trials; however a causal relationship with dapagliflozin has not been established. Dapagliflozin and saxagliptin exposures are increased in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY).

Pancreatitis: There have been post-marketing reports of acute and chronic pancreatitis in patients taking saxagliptin. Reports of fatal and non-fatal hemorrhagic or necrotizing pancreatitis were noted in patients taking other members of this class. After initiation of QTERN, patients should be observed carefully for signs and symptoms of pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, QTERN should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using QTERN. Risk factors for pancreatitis include a history of pancreatitis, gallstones, alcoholism, or hypertriglyceridemia.

Immune

Immunocompromised patients: A dose-related mean decrease in absolute lymphocyte count was observed with saxagliptin. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of QTERN on lymphocyte counts in patients with lymphocyte abnormalities (e.g. human immunodeficiency virus) is unknown. See ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings.

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Immunocompromised patients, such as patients who have undergone organ transplantation or patients diagnosed with human immunodeficiency syndrome, have not been studied in the QTERN clinical program. Therefore, the efficacy and safety profile of QTERN in these patients has not been established.

Hypersensitivity Reactions: QTERN is contraindicated in patients with a history of hypersensitivity reaction to the active substances, any of the excipients, or to any DPP4 or SGLT2 inhibitor. If a hypersensitivity reaction is suspected, discontinue QTERN, assess for other potential causes for the event, and institute alternative treatment for diabetes (see CONTRAINDICATIONS).

There have been post-marketing reports of serious hypersensitivity reactions, including anaphylaxis and angioedema, in patients treated with saxagliptin and other members of this class. Exfoliative skin conditions including Stevens-Johnson syndrome have also been reported in patients treated with saxagliptin and other members of this class, although causality with saxagliptin has not been established. Onset of these reactions occurred within the first 3 months after initiation of the treatment, with some reports occurring after the first dose (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Musculoskeletal

Severe and Disabling Arthralgia: Severe and disabling arthralgias have been reported post-marketing in patients taking saxagliptin or other DPP4 inhibitors. The onset of symptoms following initiation of drug therapy varied from one day to years. Saxagliptin is considered a possible cause for severe joint pain. Patients experienced relief of symptoms upon discontinuation of the medication and some experienced recurrence of symptoms with reintroduction of saxagliptin or another DPP4 inhibitor. If a patient treated with QTERN presents with severe joint pain, discontinuation of QTERN and replacement with other antidiabetic medications should be considered (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Renal

Renal function should be assessed prior to initiation of QTERN and periodically thereafter (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). QTERN is contraindicated, and should therefore not be initiated and should be discontinued, in patients with moderate to severe renal impairment [estimated glomerular filtration rate (eGFR) is <60 mL/min/1.73m^2] or end-stage renal disease (ESRD) (see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION).

In clinical trials, renal function abnormalities occurred after initiating QTERN. Dapagliflozin increases serum creatinine and decreases eGFR in a dose dependent fashion. Post-marketing cases of acute kidney injury, including acute renal failure, shortly after the initiation of dapagliflozin treatment have been reported. Patients with hypovolemia may be more susceptible to these changes (see ADVERSE REACTIONS).

The efficacy of dapagliflozin is dependent on renal function. In patients with moderate to severe renal impairment or ESRD, dapagliflozin did not improve glycemic control and adverse reactions were more frequent.

Skin

Ulcerative and necrotic skin lesions have been reported in monkeys in non-clinical toxicology studies with saxagliptin (see TOXICOLOGY, Acute and repeat-dose toxicity). Although skin lesions were not observed at an increased incidence in clinical trials, there is limited experience in patients with diabetic skin complications.

Rash is noted as an adverse event for saxagliptin (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). In keeping with routine care of the diabetic patient, monitoring for skin disorders is recommended.

Bullous pemphigoid: Post-marketing cases of bullous pemphigoid requiring hospitalization have been reported with the use of saxagliptin and other DPP4 inhibitors. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP4 inhibitor.

Tell patients to immediately 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.

Special Populations

Pregnant Women: QTERN must not be used in pregnancy. There are no adequate and well-controlled studies of QTERN or its monocomponents in pregnant women. When pregnancy is detected, discontinue QTERN.

In the time period corresponding to the second and third trimesters of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. (see TOXICOLOGY).

Nursing Women: QTERN must not be used by a nursing woman. It is not known whether QTERN or its monocomponents and/or their metabolites are excreted in human milk.

Studies in rats have shown excretion of dapagliflozin and saxagliptin in milk.

Exposure of dapagliflozin to weanling juvenile rats and during late pregnancy is associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. This could constitute a potential risk for human renal maturation during the first 2 years of life. Additionally, the negative effects on body-weight gain associated with lactational exposure in weanling juvenile rats suggest that dapagliflozin must be avoided during the first 2 years of life (see TOXICOLOGY).

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Pediatrics (<18 years of age): QTERN should not be used in pediatric patients. Safety and efficacy of QTERN or its monocomponents have not been established in this patient population.

Geriatrics (≥65 years of age): QTERN is not recommended in patients aged 75 years and older due to very limited experience. Use QTERN with caution in patients aged 65 years and older. Experience with QTERN in patients aged 65 years and older is limited (see INDICATIONS).

Renal function should be assessed prior to initiating QTERN and periodically thereafter in geriatric patients. Because elderly patients are more likely to have decreased renal function, care should be taken in the elderly based on renal function. Elderly patients treated with dapagliflozin had more adverse reactions related to volume depletion and renal impairment or failure, compared to patients treated with placebo. The most commonly reported adverse events related to renal impairment or failure in patients ≥65 years of age for any treatment group were creatinine renal clearance decreased, renal impairment, and increased blood creatinine (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Renal Function, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests

Blood glucose and Hemoglobin A1c (HbA1c): Response to QTERN should be monitored by periodic measurements of blood glucose and HbA1c levels.

Heart failure: Patients with a history of heart failure or other risk factors for heart failure, including renal impairment, should be closely monitored for signs and symptoms of heart failure.

Renal function: Renal function should be assessed prior to initiation of QTERN and periodically thereafter. QTERN is contraindicated in patients with an eGFR <60 mL/min/1.73 m^2.

Monitoring of renal function is recommended prior to and following initiation of any concomitant drug which might have an impact on renal function.

Reduced intravascular volume: QTERN should not be used in patients who are volume depleted (see DOSAGE AND ADMINSTRATION). Before initiating QTERN, assess volume status, particularly in patients at risk (see WARNINGS AND PRECAUTIONS, Cardiovascular, and DOSAGE AND ADMINISTRATION) as well as in case of intercurrent conditions that may lead to fluid loss (such as gastrointestinal illness) for patients already taking QTERN. In these patients, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests, including hematocrit, serum electrolytes and renal function tests) is recommended. Temporary interruption of treatment with QTERN is recommended until fluid loss is corrected.

LDL-cholesterol: LDL-C levels should be measured at baseline and at regular intervals during treatment with QTERN due to dose-dependent increases in LDL-C seen with dapagliflozin therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The 24 week, short-term (ST) pooled safety analyses comprise 1169 adults in 3 treatment groups: saxagliptin + dapagliflozin + metformin (492 subjects; data pooled from 3 phase 3 studies); saxagliptin + metformin (336 subjects data pooled from 2 studies); and dapagliflozin + metformin (341 subjects data pooled from 2 studies).

Compared to the adverse reactions identified for the respective monocomponents, no new adverse reactions for the saxagliptin + dapagliflozin combination were identified. The most commonly reported adverse reactions at 24 weeks were nasopharyngitis 3.7%, urinary tract infections (UTIs) 3.5% and headache 3.5%. The incidence of serious events regardless of causality assessment was 2.4% in the saxagliptin + dapagliflozin + metformin treatment group. One subject experienced a treatment-related serious adverse event of thrombocytopenia resulting in discontinuation of study drug. No serious events were reported in more than one subject each in the ST period. Two percent (2%) of subjects discontinued in the saxagliptin + dapagliflozin + metformin treatment group due to adverse events in the ST period. The most frequent adverse events leading to discontinuation of study treatment were glomerular filtration rate decreased (0.4%) and pollakiuria (0.4%).

With add-on treatment over 52 weeks, no new or increased safety signal was observed that had not been previously reported for each medication as monotherapy.

Saxagliptin: In a placebo-controlled clinical study of patients receiving saxagliptin 5 mg or placebo as an add-on to metformin, the incidence of serious adverse events was 9.9% and 5.6% respectively. The most commonly reported adverse events, reported regardless of causality and more common with saxagliptin than placebo, were nasopharyngitis and bronchitis. Discontinuation of therapy due to adverse events occurred in 7.3% and 4.5% of patients, respectively.

Dapagliflozin: The most commonly reported adverse events during treatment with dapagliflozin 5 mg or 10 mg (≥5%) were female genital mycotic infections, nasopharyngitis and UTIs. Discontinuation of therapy due to adverse events in patients who received dapagliflozin 5 mg and 10 mg was 2.8% and 3.2%, respectively compared to 2.5% for the placebo group. The most frequently reported events leading to discontinuation and reported in at least three (3) dapagliflozin 10 mg-treated patients were renal impairment (0.8%), decrease in creatinine clearance (0.6%), increased blood creatinine (0.3%), UTIs (0.2%), and vulvovaginal mycotic infection (0.1%).

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Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Within the QTERN clinical program, the most common adverse events regardless of causality, reported in ≥1.0% of subjects in the saxagliptin + dapagliflozin + metformin treatment group in the integrated ST Pool, are summarized in Table 1.

Table 1 Most common adverse events (reported in ≥1.0% of subjects in the Saxagliptin + Dapagliflozin + Metformin treatment group) – treated subjects[a] (Integrated 24-Week ST Pool)

	Number (%) of subjects		
System Organ Class/ Preferred term	**Saxa + Dapa + Met N=492**	**Saxa + Met N=336**	**Dapa + Met N=341**
Total subjects with an event	**250 (50.8)**	**187 (55.7)**	**157 (46.0)**
Gastrointestinal disorders			
Abdominal pain	6 (1.2)	2 (0.6)	1 (0.3)
Constipation	5 (1.0)	3 (0.9)	3 (0.9)
Diarrhea	11 (2.2)	11 (3.3)	6 (1.8)
Nausea	8 (1.6)	9 (2.7)	5 (1.5)
Infections and infestations			
Bronchitis	5 (1.0)	5 (1.5)	1 (0.3)
Gastroenteritis	6 (1.2)	3 (0.9)	3 (0.9)
Influenza	14 (2.8)	15 (4.5)	11 (3.2)
Nasopharyngitis	18 (3.7)	12 (3.6)	10 (2.9)
Upper respiratory tract infection	8 (1.6)	7 (2.1)	9 (2.6)
Urinary tract infection	17 (3.5)	18 (5.4)	13 (3.8)
Vulvovaginal mycotic infection	7 (1.4)	1 (0.3)	8 (2.3)
Investigations			
Glomerular filtration rate decreased	5 (1.0)	1 (0.3)	2 (0.6)
Metabolism and nutrition disorders			

Dyslipidemia	11 (2.2)	8 (2.4)	7 (2.1)
Hypercholesterolemia	6 (1.2)	1 (0.3)	2 (0.6)
Hypertriglyceridemia	11 (2.2)	13 (3.9)	9 (2.6)
Musculoskeletal and connective tissue disorders			
Arthralgia	12 (2.4)	4 (1.2)	3 (0.9)
Back pain	13 (2.6)	8 (2.4)	6 (1.8)
Nervous system disorders			
Headache	17 (3.5)	14 (4.2)	10 (2.9)
Renal and urinary disorders			
Pollakuria	7 (1.4)	1 (0.3)	4 (1.2)
Respiratory, thoracic and mediastinal disorders			
Cough	7 (1.4)	6 (1.8)	3 (0.9)

[a]Treated subjects were those who received at least 1 dose of double-blind study treatment during the ST, double blind treatment.
All listed events were treatment emergent, which was defined as non-serious or serious adverse events with an onset from Day 1 of the ST double-blind treatment up to and including 4 days (for adverse events) and 30 days (for serious adverse events) after the last dose date in the ST double-blind treatment period.

In the 52-week long term (LT) extensions of individual studies, the most common adverse events reported with saxagliptin + dapagliflozin + metformin treatment were similar to those observed during the ST phase.

Less Common Clinical Trial Adverse Drug Reactions (other than events listed in Table 1 above) Reported in <1% of Subjects Treated with Saxagliptin + Dapagliflozin + Metformin during 24-Week ST Period

Gastrointestinal disorders: Dry mouth, Vomiting

Infections and infestations: Sinusitis, Vaginal infection

Investigations: Weight decreased

Nervous system disorders: Dizziness

Renal and urinary disorders: Dysuria, Polyuria

Reproductive and breast disorders: Vulvovaginal pruritus

Skin and subcutaneous tissue disorders: Rash

Note: for a complete listing of common and less common adverse reactions within the saxagliptin and within the dapagliflozin clinical trial programs, consult the individual Product Monographs.

Description of Selected Adverse Reactions

Cardiovascular Safety

In the ST pooled analyses, cardiovascular (CV) events that were adjudicated and confirmed as CV events were reported in a total of 0.8% of subjects in the saxagliptin + dapagliflozin + metformin group, 0.6% in the saxagliptin + metformin group, and 0.6% in the dapagliflozin + metformin group. No adjudicated CV event was considered treatment-related (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Saxagliptin: The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial was a CV outcome trial in 16,492 type 2 diabetic patients (median HbA1c = 7.6%) (12,959 with established CV disease; 3533 with multiple risk factors only) who were randomized to saxagliptin (n=8280) or placebo (n=8212). The study population also included those ≥65 years (n=8561) and ≥75 years (n=2330), with normal or mild renal impairment (n=13,916) as well as moderate (n=2240) or severe (n=336) renal impairment. Subjects were followed for a mean duration of 2 years.

The primary endpoint was a composite endpoint consisting of the time-to-first occurrence of any of the following major adverse CV events (MACE): CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke.

The trial established that the upper bound of the 2-sided 95% CI for the estimated risk ratio comparing the incidence of the primary composite endpoint observed with saxagliptin to that observed in the placebo group was <1.3. The study did not demonstrate the superiority of saxagliptin compared with placebo when added to current background therapy, in reducing the primary MACE endpoint (HR 1.00; 95% CI: 0.89, 1.12; p = 0.986).

Hospitalization for heart failure, occurred at a greater rate in the saxagliptin group (3.5%) compared with the placebo group (2.8%) [HR = 1.27; (95% CI 1.07, 1.51)]. Subjects on saxagliptin with a baseline history of congestive heart failure, especially those who also had renal impairment and/or MI, were at higher absolute risk for hospitalization for heart failure.

Dapagliflozin: A meta-analysis of cardiovascular events across placebo-controlled studies was performed. The number of subjects per treatment was 4016 for dapagliflozin 5/10 mg and 2776 for placebo. Cardiovascular events were adjudicated by an independent adjudication committee. The primary endpoint was the time to first event of the following outcomes: cardiovascular death, stroke, myocardial infarction, and hospitalization for unstable angina. Primary events occurred at a rate of 1.86% per 100 patient-years in patients treated with dapagliflozin 5/10 mg/day and 2.41% in placebo-treated patients, per 100 patient-years. The hazard ratio comparing dapagliflozin to placebo was 0.77 (95% confidence interval; 0.55, 1.07). Therefore, there was no evidence of an increase in the primary endpoint with dapagliflozin 5 mg/10 mg relative to placebo.

Diabetic Ketoacidosis

Cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes treated with dapagliflozin and other SGLT2 inhibitors. Some cases of DKA have been fatal. QTERN is not indicated, and should not be used, in patients with type 1 diabetes. In some cases, the presentation of the condition was atypical, with blood glucose values only moderately elevated (<13.9 mmol/L (250 mg/dL); see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions, Endocrine and Metabolism).

Genital Infections

The reported adverse drug reactions of genital infection, including vulvovaginal mycotic infection, vulvovaginal candidiasis, balanoposthisis and related genital infections from the ST pooled safety analysis were reflective of the adverse events with dapagliflozin. The proportion of subjects who reported an adverse event of genital infection in the pooled safety analysis was higher in the 2 dapagliflozin-containing treatment groups: 4.1% in the dapagliflozin + metformin group and 1.6% in the saxagliptin + dapagliflozin + metformin group compared to 0.6% in the saxagliptin + metformin group (see WARNINGS AND PRECAUTIONS, Genitourinary).

Dapagliflozin: Events of genital mycotic infections were reported in 5.7%, 4.8%, and 0.9% of patients who received dapagliflozin 5 mg, dapagliflozin 10 mg and placebo, respectively, in a 12-study, ST, placebo-controlled pool. Infections were more frequently reported in females than in males, and in patients who had a previous history of recurrent genital mycotic infections. The most frequently reported genital infections were vulvovaginal mycotic infections in females, and balanitis in males.

Hypoglycemia

In the ST pooled safety analysis, hypoglycemic events were reported in 1.2% of patients in the saxagliptin + dapagliflozin + metformin group, 0.3% of patients in the saxagliptin + metformin group, and 1.8% of patients in the dapagliflozin + metformin group. None of the reported hypoglycemia events was a major episode, and no subject discontinued the study treatment due to hypoglycemia.

Malignancies

Dapagliflozin: Across 22 dapagliflozin clinical studies, newly diagnosed cases of bladder cancer were reported in 10/6045 patients (0.17%) treated with dapagliflozin and 1/3512 patient (0.03%) treated with placebo/comparator. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 4 cases with dapagliflozin and no cases with placebo/comparator. Bladder cancer risk factors (e.g. smoking, age) and hematuria (a potential indicator of pre-existing tumors) were balanced between treatment arms at baseline. There were too few cases to determine whether the emergence of these events is related to dapagliflozin (see WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

Renal Function Decreased

In the ST pooled safety analysis, the incidence of adverse events of renal impairment/failure was reported in 7 subjects (1.4%) in the saxagliptin + dapagliflozin + metformin group, 6 subjects (1.8%) in the saxagliptin + metformin group, and 2 subjects (0.6%) in the dapagliflozin + metformin group.

Among these subjects, adverse events with the preferred term "glomerular filtration rate decreased" were reported in 5 (1.0%) subjects in the saxagliptin + dapagliflozin + metformin group, 1 (0.3%) subject in the saxagliptin + metformin group, and 2 (0.6%) subjects in the dapagliflozin + metformin group.

The change in mean estimated glomerular filtration rate (eGFR) from baseline at Week 24 was -1.17 mL/min/1.73m^2 in the saxagliptin + dapagliflozin + metformin group, -0.46 mL/min/1.73 m^2 in saxagliptin + metformin, and 0.81 mL/min/1.73m^2 in dapagliflozin + metformin (see WARNINGS AND PRECAUTIONS, Renal).

Dapagliflozin: Safety was also assessed in a dedicated study of diabetic patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m^2). At Week 52, dapagliflozin was associated with changes from baseline in mean eGFR (eGFR: dapagliflozin 5 mg: -2.08 mL/min/1.73m^2, dapagliflozin 10 mg -4.46 mL/min/1.73m^2 and placebo -2.58 mL/min/1.73m^2). At Week 104, these changes persisted (eGFR: dapagliflozin 5 mg -1.71 mL/min/1.73m^2, dapagliflozin 10 mg -3.50 mL/min/1.73m^2 and placebo -2.38 mL/min/1.73 m^2). With dapagliflozin 5 mg and 10 mg, these eGFR reductions were evident at Week 1 while placebo treated patients had a slow continuous decline through Week 104. At Week 52 and persisting through Week 104, greater increases in mean parathyroid hormone and serum phosphorus were observed in this study with dapagliflozin 5 mg and 10 mg compared to placebo, where baseline values of these analytes were higher.

Overall, there were 13 patients with an adverse event of bone fracture reported in this study up to Week 104 of which 8 occurred in the dapagliflozin 10 mg group, 5 occurred in the dapagliflozin 5 mg group, and none occurred in the placebo group. Eight of these 13 fractures were in patients who had eGFR 30 to 45 mL/min/1.73 m^2 and 11 of the 13 fractures were reported within the first 52 weeks.

Urinary Tract Infections

In the pooled ST safety analysis, UTIs were frequently reported across the 3 treatment groups: 3.5% in the saxagliptin + dapagliflozin + metformin group, 5.7% in the saxagliptin + metformin group and 3.8% in the dapagliflozin + metformin group. Across all the three treatment groups, the incidence of UTIs was higher in females than males. One male patient in the saxagliptin + dapagliflozin + metformin group experienced a treatment-related serious adverse event of pyelonephritis that resulted in discontinuation during the LT extension (see WARNINGS AND PRECAUTIONS, Genitourinary).

Dapagliflozin: Events of urinary tract infections were reported in 5.7%, 4.3%, and 3.7% of patients who received dapagliflozin 5 mg, dapagliflozin 10 mg and placebo, respectively, in the 12-study, ST, placebo-controlled pool. Infections were more frequently reported in females (9.6% and 7.7% dapagliflozin 5 mg and 10 mg, respectively, vs. 6.6% placebo) than in males (1.6% and 0.8% dapagliflozin 5 mg and 10 mg, respectively, vs. 1.0% placebo).

In 9 of the 13 studies in the dapagliflozin 10 mg placebo-controlled pool for which LT treatment data were available, of the 174 patients treated with dapagliflozin 10 mg who experienced an infection, 135 (77.6%) had only one and 11 (6.3%) had 3 or more. Of the 121 patients treated with placebo who experienced an infection, 94 (77.7%) had only one and 12 (9.9%) had 3 or more.

In the 13-study, ST, placebo-controlled pool, patients who had a previous history of recurrent urinary tract infection, were more likely to have an event of urinary tract infection during the study than those without a history of infection.

Volume Depletion

The reported adverse events of hypotension, dehydration, and hypovolemia from the ST pooled safety analysis were reflective of the adverse events with dapagliflozin. The frequency of adverse events of hypotension, dehydration, and hypovolemia was infrequent in the ST pooled safety analysis, with events reported in 2 (0.6%) subjects with dapagliflozin plus metformin group (1 adverse event each of hypotension and syncope). Neither adverse event was reported as serious, or resulted in discontinuation of study medication (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Dapagliflozin: Events related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) were reported in 0.6%, 0.8% and 0.4% of patients who received dapagliflozin 5 mg, dapagliflozin 10 mg and placebo, respectively, in the 12-study, ST, placebo-controlled pool. In subgroup analyses of patients on loop diuretics or ≥65 years of age in the 13-study placebo-controlled pool, the proportions of patients with events related to volume depletion were higher in patients treated with dapagliflozin 10 mg than in those treated with placebo (events in patients on loop diuretics: 2.5% vs. 1.5%; events in patients ≥65 years of age: 1.7% vs. 0.8%, respectively).

Postural blood pressure measurement revealed orthostatic hypotension in 13.1% of patients treated with dapagliflozin 10 mg vs. 11.3% of patients treated with placebo over the 24-week treatment period.

Abnormal Hematologic and Clinical Chemistry Findings

Creatine kinase (CK): In the pooled ST safety analysis, a higher proportion of subjects treated with saxagliptin + dapagliflozin + metformin had CK values >5X upper limit of normal (ULN) (1.2%) and >10X ULN (0.8%) compared to 0 subjects in the saxagliptin + metformin and dapagliflozin + metformin groups.

Serum potassium: In the pooled ST safety analysis, a higher proportion of subjects in the saxagliptin + dapagliflozin + metformin group (2.3%) had high (≥6.0 mEq/L) serum potassium compared with the saxagliptin + metformin (0.9%) and dapagliflozin + metformin (1.2%) groups.

Saxagliptin

Absolute Lymphocyte Counts: A dose-related mean decrease in absolute lymphocyte count was observed with saxagliptin. From a baseline absolute lymphocyte count of approximately 2200 cells/µL, a mean decrease of approximately 100 cells/µL relative to placebo was observed in a pooled analysis of the placebo-controlled clinical studies. The proportion of patients who were reported to have a lymphocyte count ≤ 750 cells/µL was 1.5% in the saxagliptin 5 mg group and 0.4% in the placebo group. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of saxagliptin on lymphocyte counts in patients with lymphocyte abnormalities (e.g. human immunodeficiency virus) is unknown.

Platelets: Saxagliptin did not demonstrate a clinically meaningful or consistent effect on platelet count in the double-blind, controlled clinical safety and efficacy trials. In the add-on to insulin trial, there was a -2.6% decrease from baseline in platelet count in the saxagliptin group compared with a -0.1% decrease in the placebo group. An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to saxagliptin is not known.

Urinary white and red blood cell counts: In the add-on to insulin trial, there was a higher percentage of saxagliptin patients, compared to placebo patients who presented with marked urinary red blood cell counts (15.1% saxagliptin versus 3.2% placebo) and urinary white blood cell counts (30.4% versus 18.9%). No consistent findings of urine laboratory abnormalities have been observed in the overall saxagliptin clinical program. No imbalances were observed for either URBC or UWBC in the pooled analysis of Phase 2/3 studies.

Dapagliflozin

Increases in serum creatinine, blood urea nitrogen (BUN) and decreased eGFR*:* In the pool of 13 placebo-controlled studies, in dapagliflozin-treated patients, mean eGFR decreased by Week 1 and then increased toward eGFR baseline values over time to Week 24.

Changes from baseline in serum creatinine were consistent with changes in eGFR. Mean serum creatinine levels increased at Week 1 and decreased toward baseline at Week 24. There were small increases in BUN. Mean BUN levels increased at Week 1 and values remained stable through Weeks 24 and 102.

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Table 2 Mean Changes from Baseline for Serum Creatinine and eGFR at Week 1 and Week 24

Study Week/ Treatment Group	Week 1*		Week 24*	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
Serum creatinine, µmol/L (mg/dL)				
Mean Changes from Baseline	-3.62 (-0.041) N=1112	-0.71 (-0.008) N=1057	1.68 (0.019) N=1954	0.71 (0.008) N=1844
eGFR, mL/min/1.73m^2				
Mean Changes from Baseline	-4.174 N=1102	0.490 N=1048	-1.446 N=1954	-0.665 N=1844

*Pool of 13 placebo-controlled studies

Increases in Hemoglobin/Hematocrit: In the pool of 13 placebo-controlled studies, increases from baseline in mean hemoglobin values were observed and increases from baseline in mean hematocrit values were observed in dapagliflozin-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. The mean changes from baseline in hemoglobin and hematocrit at Weeks 24 and 102 are presented below.

Table 3 Mean Changes from Baseline for Hemoglobin and Hematocrit at Week 24 and Week 102

Study Week/ Treatment Group	Week 24*		Week 102**	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
Hemoglobin, g/L (g/dL)				
Mean Changes from Baseline	6.21 (0.621) N=1934	- 1.38 (-0.138) N=1828	7.0 (0.70) N=621	-2.1 (-0.21) N=515
Hematocrit, %				
Mean Changes from Baseline	2.30 N=1908	-0.33 N=1796	2.68 N=616	-0.46 N=510

*Pool of 13 placebo-controlled studies

**Pool of 9 placebo-controlled studies

By Week 24, hematocrit values >55% were reported in 1.3% of dapagliflozin 10 mg-treated patients vs. 0.4% of placebo-treated patients. Results were similar during the ST plus LT phase (the majority of patients were exposed to treatment for more than one year).

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Increases in Serum Inorganic Phosphorus: In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin 10 mg-treated patients compared with placebo-treated patients. Similar results were seen at Week 102 (see Table 4). Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia were reported in dapagliflozin 10 mg group vs. placebo at Week 24 and during the ST plus LT phase. The clinical relevance of these findings is unknown.

Table 4 Mean Changes from Baseline for Serum Inorganic Phosphorus and Proportion of Patients with Hyperphosphatemia at Week 24 and Week 102

Study Week/ Treatment Group	Week 24*		Week 102**	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
Serum Inorganic Phosphorus, µmol/L (mg/dL)				
Mean Changes from Baseline	42.0 (0.13) N=1954	-12.9 (-0.04) N=1844	38.7 (0.12) N=627	6.5 (0.02) N=522
Hyperphosphatemia†				
Proportion of Patients	1.7% N=1178	0.7% N=1381	3.0% N=2001	1.6% N=1940

*Pool of 13 placebo-controlled studies
**Pool of 9 placebo-controlled studies
†Defined as ≥1.81 mmol/L (≥5.6 mg/dL) if age 17 - 65 or ≥1.65 mmol/L (≥5.1 mg/dL) if ≥ age 66

Lipids: In the pool of 13 placebo-controlled studies, increases from baseline were noted in levels of total cholesterol, LDL- and HDL-cholesterol, and decreases from baseline were noted for triglycerides at Week 24 and Week 102 in dapagliflozin 10 mg-treated patients compared with placebo-treated patients (see Table 5).

Table 5 Mean Changes from Baseline for Lipid Parameters at Week 24 and Week 102

Study Week/ Treatment Group	Week 24*		Week 102**	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
Mean Percent Changes from Baseline				
Total Cholesterol	2.5% N=1851	0.0% N=1747	2.1% N=550	-1.5% N=446
HDL-cholesterol	6.0% N=1851	2.7% N=1748	6.6% N=549	2.1% N=447

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LDL-cholesterol	2.9% N=1840	-1.0% N=1736	2.9% N=542	-2.2% N=442
Triglycerides	-2.7% N=1844	-0.7% N=1736	-1.8% N=545	-1.8% N=444

*Pool of 13 placebo-controlled studies
**Pool of 9 placebo-controlled studies

The ratio between LDL-cholesterol and HDL-cholesterol decreased for both treatment groups at Week 24 and at Week 102.

Post-Market Adverse Drug Reactions

Additional adverse reactions have been identified during post-marketing use of saxagliptin and dapagliflozin. Because these 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.

Saxagliptin

Blood and lymphatic system disorders: idiopathic thrombocytopenic purpura

Gastrointestinal disorders: acute and chronic pancreatitis (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)

Immune system disorders: hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria and exfoliative skin conditions, including Stevens-Johnson syndrome (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Immune)

Musculoskeletal and connective tissue disorders: severe and disabling arthralgia (see WARNINGS AND PRECAUTIONS, Musculoskeletal), rhabdomyolysis.

Skin and subcutaneous tissue disorders: bullous pemphigoid

Dapagliflozin

Genitourinary: severe urinary tract infections, urosepsis and pyelonephritis

Metabolism: diabetic ketoacidosis

Renal and urinary disorders: acute kidney injury, including acute renal failure

Skin and subcutaneous tissue disorders: rash (including rash generalized, rash pruritic, rash macular, rash macular-papular, rash pustular and rash vascular)

DRUG INTERACTIONS

Overview

Specific pharmacokinetic drug interactions studies with QTERN have not been performed, although such studies have been conducted with the individual saxagliptin and dapagliflozin components.

The lack of pharmacokinetic interaction between saxagliptin and dapagliflozin was demonstrated in a drug-drug interaction study between saxagliptin 5 mg and dapagliflozin 10 mg.

See saxagliptin and dapagliflozin subsections for drug interactions.

Saxagliptin: The metabolism of saxagliptin is primarily mediated by P450 3A4/5 (CYP3A4/5). In *in vitro* studies, saxagliptin and its major pharmacologically active metabolite neither inhibited nor induced CYP3A4. In addition, in *in vitro* studies, saxagliptin and its major pharmacologically active metabolite neither inhibited CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, nor induced CYP1A2, 2B6, 2C9. Therefore, saxagliptin is unlikely to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is neither a significant inhibitor of P-glycoprotein (P-gp) nor an inducer of P-gp, and is unlikely to cause interactions with drugs that utilize these pathways.

The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is below measurable levels. Thus, protein binding would not have a meaningful influence on the pharmacokinetics of saxagliptin or other drugs.

Dapagliflozin: The metabolism of dapagliflozin is primarily mediated by UGT1A9-dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor.

In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

Drug-Drug Interactions

Saxagliptin and dapagliflozin are components of QTERN. Coadministration of a single dose of saxagliptin (5 mg) and dapagliflozin (10 mg) did not affect the pharmacokinetics of each other (Table 6).

Table 6 Effect of Coadministration of Saxagliptin (5 mg) and Dapagliflozin (10 mg) on the Systemic Exposure of Each Other

Effect of Saxagliptin on Dapagliflozin Exposure Ratio of Adjusted Geometric Means (90% CI)		Effect of Dapagliflozin on Saxagliptin Exposure Ratio of Adjusted Geometric Means (90% CI)	
Cmax	AUC(INF)	Cmax	AUC(INF)
0.943 (0.867, 1.026)	0.984 (0.961, 1.008)	0.927 (0.883, 0.972)	0.991 (0.961, 1.022)

Saxagliptin

Effect of other drugs on saxagliptin

CYP3A4/5 Inducers: The coadministration of saxagliptin and CYP3A4/5 inducers, other than rifampin (such as carbamazepine, dexamethasone, phenobarbital and phenytoin) have not been studied and may result in decreased plasma concentration of saxagliptin and increased concentration of its major metabolite. Glycemic control should be carefully assessed when QTERN is used with a potent CYP3A4 inducer.

Metformin: Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an OCT-1 and OCT-2 substrate, decreased the C_{max} of saxagliptin by 21%; however, the AUC was unchanged. Therefore, metformin is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin with other OCT-1 and OCT-2 substrates would not be expected.

Glyburide: Coadministration of a single dose of saxagliptin (10 mg) and glyburide (5 mg), a CYP2C9 substrate, did not affect the pharmacokinetics of saxagliptin. Meaningful interactions of saxagliptin with other CYP2C9 substrates would not be expected. Glyburide is **not indicated** in combination with QTERN.

Pioglitazone: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 (major) and CYP3A4 (minor) substrate, did not alter the pharmacokinetics of saxagliptin. Meaningful interactions of saxagliptin with other CYP2C8 substrates would not be expected. Pioglitazone is **not indicated** in combination with QTERN (see WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

Ketoconazole: Coadministration of a single dose of saxagliptin (100 mg) and ketoconazole (200 mg every 12 hours at steady state), a potent inhibitor of CYP3A4/5 and P-gp, increased the C_{max} and AUC for saxagliptin by 62% and 145% respectively. This coadministration was also associated with 95% and 88% decreases in C_{max} and AUC(INF) values, respectively of its major metabolite.

Following coadministration of a single dose of saxagliptin at 20 times the recommended dose (100 mg) with ketoconazole, transient flu-like symptoms and a transient decrease in absolute lymphocyte count were observed. Additionally, transient decreases in absolute lymphocyte count were observed without any flu-like symptoms following coadministration of a single dose of saxagliptin at 4 times the recommended dose (20 mg) with ketoconazole.

Rifampin (Rifampicin): Coadministration of a single dose of saxagliptin (5 mg) with the potent CYP3A4/5 and P-gp inducer rifampin (600 mg once daily at steady state), decreased the C_{max} and AUC of saxagliptin by 53% and 76%, respectively. There was a corresponding increase in C_{max} (39%) but no significant change in plasma AUC of the active metabolite. There was no change in the maximum DPP4 inhibition (%Imax) and only a 6% decrease in the mean area under the effect time curve for DPP4 inhibition (AUEC) over a 24-hour period (the dosing interval for saxagliptin) when saxagliptin was coadministered with rifampin; however, a shorter DPP4 inhibition T-HALF was observed during the rifampin

coadministration period (25.9 hours for saxagliptin-alone versus 14.5 hours for saxagliptin plus rifampin).

Digoxin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of saxagliptin. Therefore, digoxin is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin with other P-gp substrates would not be expected.

Simvastatin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, increased the C_{max} of saxagliptin by 21%; however, the AUC of saxagliptin was unchanged. Therefore, simvastatin is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin would not be expected with other substrates of CYP3A4/5.

Diltiazem: Coadministration of a single dose of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the C_{max} and AUC for saxagliptin by 63% and 109%, respectively. This coadministration was also associated with 44% and 34% decreases in C_{max} and AUC(INF) values, respectively of its major metabolite. Therefore, diltiazem is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin with other moderate CYP3A4/5 inhibitors would not be expected.

Glyemic control should be carefully assessed when QTERN is used concomitantly with a potent CYP3A4 inducer. Using CYP3A4 inducers like carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampin may reduce the glycemic lowering effect of QTERN (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Omeprazole: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and omeprazole (40 mg), a CYP2C19 (major) and CYP3A4 substrate, an inhibitor of CYP2C19, and an inducer of MRP-3, did not alter the pharmacokinetics of saxagliptin. Therefore, omeprazole is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin with other CYP2C19 inhibitors or MRP-3 inducers would not be expected.

Aluminum hydroxide + magnesium hydroxide + simethicone: Coadministration of a single dose of saxagliptin (10 mg) and a liquid containing aluminum hydroxide (2400 mg), magnesium hydroxide (2400 mg), and simethicone (240 mg) decreased the C_{max} of saxagliptin by 26%; however, the AUC of saxagliptin was unchanged. Therefore, meaningful interactions of saxagliptin with antacid and antigas formulations of this type would not be expected.

Famotidine: Administration of a single dose of saxagliptin (10 mg) three hours after a single dose of famotidine (40 mg), an inhibitor of hOCT-1, hOCT-2, and hOCT-3, increased the C_{max} of saxagliptin by 14%; however, the AUC of saxagliptin was unchanged. Therefore, famotidine is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin would not be expected with other inhibitors of hOCT-1, hOCT-2, and hOCT-3.

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Effect of saxagliptin on other drugs

Metformin: Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an OCT-1 and OCT-2 substrate, did not alter the pharmacokinetics of metformin in healthy subjects. Therefore, saxagliptin is considered unlikely to cause a clinically meaningful interaction with metformin. Saxagliptin is not an inhibitor of OCT-1 and OCT-2- mediated transport.

Glyburide: Coadministration of a single dose of saxagliptin (10 mg) and glyburide (5 mg), a CYP2C9 substrate, increased the plasma C_{max} of glyburide by 16%; however, the AUC of glyburide was unchanged. Saxagliptin does not meaningfully inhibit CYP2C9-mediated metabolism. QTERN is **not indicated** in combination with glyburide.

Pioglitazone: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 substrate, increased the plasma C_{max} of pioglitazone by 14%; however, the AUC of pioglitazone was unchanged. Saxagliptin does not meaningfully inhibit or induce CYP2C8-mediated metabolism. QTERN is **not indicated** in combination with pioglitazone (see WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

Digoxin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of digoxin. Therefore, saxagliptin is considered unlikely to cause a clinically meaningful interaction with digoxin. Saxagliptin is not an inhibitor or inducer of P-gp-mediated transport.

Simvastatin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, did not alter the pharmacokinetics of simvastatin. Therefore, saxagliptin is considered unlikely to cause a clinically meaningful interaction with simvastatin. Saxagliptin is not an inhibitor or inducer of CYP3A4/5-mediated metabolism.

Diltiazem: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the plasma C_{max} of diltiazem by 16%; however, the AUC of diltiazem was unchanged. Therefore, saxagliptin is considered unlikely to cause a clinically meaningful interaction with diltiazem.

Ketoconazole: Coadministration of a single dose of saxagliptin (100 mg) and multiple doses of ketoconazole (200 mg every 12 hours at steady state), a potent inhibitor of CYP3A4/5 and P-gp, decreased the geometric means for C_{max} and AUC(INF) of ketoconazole by 16% and by 13% respectively, relative to those observed following administration of 200 mg ketoconazole q 12 h alone.

Oral Contraceptives: Coadministration of multiple once-daily doses of saxagliptin (5 mg) and a monophasic combined oral contraceptive containing 0.035 mg ethinyl estradiol/0.250 mg norgestimate for 21 days, did not alter the steady state pharmacokinetics of the primary active estrogen component, ethinyl estradiol, or the primary active progestin component, norelgestromin. The plasma AUC of norgestrel, an active metabolite of norelgestromin, was

increased by 13% and the plasma C_{max} of norgestrel was increased by 17%. This small magnitude change in AUC and C_{max} of norgestrel is not considered to be clinically meaningful. Based on these findings, saxagliptin would not be expected to meaningfully alter the pharmacokinetics of an estrogen/progestin combined oral contraceptive.

Dapagliflozin

Effect of other drugs on dapagliflozin

In studies conducted in healthy subjects, the pharmacokinetics of dapagliflozin were not altered by the coadministered drugs (see Table 7).

Table 7 Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure

Coadministered Drug (Dose Regimen)*	**Dapagliflozin** (Dose Regimen)*	**Effect on Dapagliflozin Exposure Ratio of Adjusted Geometric Means (90% CI)**		**Clinical Comment**
		Cmax	**AUC†**	
Oral Antidiabetic Agents				
Metformin (1000 mg)	20 mg	0.932 (0.848, 1.024	0.995 (0.945, 1.053)	No dosing adjustment required
Pioglitazone (45 mg)	50 mg	1.09 (1.00, 1.18)	1.03 (0.98, 1.08)	**Not indicated††**
Sitagliptin (100 mg)	20 mg	0.958 (0.875, 1.049)	1.081 (1.031, 1.133)	**Do not use**
Glimepiride (4 mg)	20 mg	1.006 (0.921, 1.097)	0.989 (0.958, 1.020)	**Not indicated**
Other Medications				
Hydrochlorothiazide (25 mg)	50 mg	NC	1.07 (1.04, 1.11)	No dosing adjustment required
Bumetanide (1 mg)	10 mg once daily for 7 – 14 days	1.080 (0.953, 1.222)	1.047 (0.991, 1.106)	No dosing adjustment required
Valsartan (320 mg)	20 mg	0.881 (0.796, 0.975)	1.024 (1.000, 1.049)	No dosing adjustment required
Simvastatin (40 mg)	20 mg	0.978 (0.887, 1.078)	0.986 (0.957, 1.017)	No dosing adjustment required

Table 7 Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Dapagliflozin Exposure Ratio of Adjusted Geometric Means (90% CI)		Clinical Comment
		Cmax	AUC†	
Mefenamic acid (250 mg every 6 hours)	10 mg	1.13 (1.03, 1.24)	1.51 (1.44, 1.58)	No dosing adjustment required
Anti-infective Agent				
Rifampin (600 mg once daily for 6 days)**	10 mg	0.931 (0.779, 1.112)	0.780 (0.731, 0.832)	No dosing adjustment required

* Single dose unless otherwise noted.
NC No apparent change, ratio and 90% CI were not calculated.
† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.
** The mean amount of glucose excreted in the urine over 24 h following administration of dapagliflozin alone (51 g) was not markedly affected by rifampin coadministration (45 g).
†† See WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis.

Effect of dapagliflozin on other drugs

In studies conducted in healthy subjects, as described below, dapagliflozin did not alter the pharmacokinetics of the coadministered drugs (see Table 8).

Table 8 Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Coadministered Drug Exposure Ratio of Adjusted Geometric Means (90% CI)		Clinical Comment
		Cmax	AUC†	
Oral Antidiabetic Agents				
Metformin (1000 mg)	20 mg	0.953 (0.866, 1.049)	1.001 (0.933, 1.075)	No dosing adjustment required
Pioglitazone (45 mg)	50 mg	0.93 (0.75, 1.15)	1.00 (0.90, 1.13)	**Not indicated**††
Sitagliptin (100 mg)	20 mg	0.887 (0.807, 0.974)	1.012 (0.985, 1.040)	**Do not use**
Glimepiride (4 mg)	20 mg	1.043 (0.905, 1.201)	1.132 (0.996, 1.287)	**Not indicated**

Table 8 Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Coadministered Drug Exposure Ratio of Adjusted Geometric Means (90% CI)		Clinical Comment
		Cmax	AUC†	
Other Medications				
Hydrochlorothiazide (25 mg)	50 mg	NC	0.99 (0.95, 1.04)	No dosing adjustment required
Bumetanide (1 mg)**	10 mg once daily for 7 days	1.132 (0.979, 1.310)	1.132 (0.985, 1.302)	No dosing adjustment required
Valsartan (320 mg)	20 mg	0.938 (0.762, 1.156)	1.046 (0.850, 1.286)	No dosing adjustment required
Simvastatin (40 mg)	20 mg	0.936 (0.816, 1.073)	1.193 (1.018, 1.399)	No dosing adjustment required
Digoxin (0.25 mg)	20 mg loading dose then 10 mg once daily for 7 days	0.990 (0.843, 1.162)	1.002 (0.860, 1.167)	No dosing adjustment required
Warfarin (25 mg)***	20 mg loading dose then 10 mg once daily for 7 days	S-warfarin 1.030 (0.994, 1.124) R-warfarin 1.057 (0.977, 1.145)	 1.068 (1.002, 1.138) 1.079 (1.030, 1.130)	No dosing adjustment required

* Single dose unless otherwise noted.
NC No apparent change, ratio and 90% CI were not calculated.
† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.
** Coadministration of dapagliflozin did not meaningfully alter the steady-state pharmacodynamic responses (urinary sodium excretion, urine volume) to bumetanide in healthy subjects.
*** Dapagliflozin also did not affect the anticoagulant activity of warfarin as measured by the prothrombin time (International Normalized Ratio; [INR]).
†† See WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis.

Pharmacodynamic Interactions

Diuretics: QTERN should be used with caution in patients taking diuretics, particularly loop diuretics, due to the increased risk of adverse events due to volume depletion (see

WARNINGS AND PRECAUTIONS, Cardiovascular; ADVERSE REACTIONS, Description of Selected Adverse Reactions).

Drug-Food Interactions

Saxagliptin: There are no known interactions with food. Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism may give rise to modest increases in plasma levels of saxagliptin.

Dapagliflozin: Interactions with food have not been studied (see ACTION AND CLINICAL PHARMACOLOGY).

Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort (Hypericum perforatum) is a CYP3A4 inducer and coadministration with QTERN may result in loss of efficacy or reduced clinical response.

Drug-Laboratory Interactions

Due to its mechanism of action, patients taking dapagliflozin, a component of QTERN, will test positive for glucose in their urine.

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Drug-Lifestyle Interactions

The effects of smoking, diet, and alcohol use on the pharmacokinetics of saxagliptin and dapagliflozin have not been specifically studied.

No studies on the effects of saxagliptin and dapagliflozin on the ability to drive and use machines have been performed. When driving or using machines, it should be taken into account that dizziness has been reported in studies with the combined use of saxagliptin and dapagliflozin. QTERN is not indicated in combination with insulin or an insulin secretagogue, such as a sulfonylurea, which could increase the risk of hypoglycemia.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Antihyperglycemic agents: The safety and efficacy of this medicine in combination with glucagon-like peptide 1 (GLP-1) analogues, insulin and its analogues, or sulphonylurea has not been established (see INDICATIONS, WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Diuretics: QTERN should be used with caution in patients taking diuretics, particularly loop diuretics, due to the increased risk of adverse events due to volume depletion (see

WARNINGS AND PRECAUTIONS, Cardiovascular; ADVERSE REACTIONS, Description of Selected Adverse Reactions).

Recommended Dose and Dosage Adjustment

For patients inadequately controlled on metformin and saxagliptin alone, the recommended starting dose of QTERN is one 5 mg saxagliptin/5 mg dapagliflozin tablet taken once daily at any time of the day with or without food. In patients tolerating QTERN 5 mg/5 mg once daily, the dose can be increased to 5 mg/10 mg daily (see CLINICAL TRIALS).

Patients switching from separate tablets of saxagliptin and dapagliflozin to QTERN should receive the same daily dose of saxagliptin and dapagliflozin already being taken.

Tablets are to be swallowed whole.

In patients with evidence of volume depletion, this condition should be corrected prior to initiation of QTERN (see WARNINGS AND PRECAUTIONS).

Renal Impairment: Renal function should be assessed prior to initiation of QTERN treatment and periodically thereafter. Efficacy is dependent on renal function. QTERN can be administered to patients with mild renal impairment (eGFR ≥60 mL/min/1.73m^2).

QTERN should be discontinued when eGFR is <60 mL/min/1.73m^2 (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

QTERN is contraindicated in patients with moderate to severe renal impairment (defined as eGFR <60 mL/min/1.73m^2) or ESRD (see CONTRAINDICATIONS). In such patients dapagliflozin did not improve glycemic control, and adverse reactions were more frequent.

Hepatic Impairment: QTERN can be administered to patients with mild hepatic impairment. Use in moderate to severe hepatic impairment is not recommended (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Pediatrics (<18 years of age): Safety and effectiveness of QTERN or its monocomponents in pediatric patients have not been established. Therefore, QTERN should not be used in this patient population.

Geriatrics (≥65 years of age): No dosage adjustment is recommended for QTERN on the basis of age. QTERN is not recommended in patients aged 75 years and older due to very limited experience. Use QTERN with caution in patients aged 65 years and older. Because elderly patients are more likely to have decreased renal function, care should be taken in the elderly based on renal function (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Missed Dose

If a dose of QTERN is missed, it should be taken as soon as the patient remembers. A double dose of QTERN should not be taken on the same day.

OVERDOSAGE

There is no information available on overdose with QTERN (saxagliptin/dapagliflozin).

Saxagliptin: In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its major metabolite are removed by hemodialysis (23% of dose over four hours).

Dapagliflozin: It is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

QTERN (saxagliptin/dapagliflozin) combines saxagliptin and dapagliflozin with distinct and complementary mechanisms of action to improve glycemic control. Saxagliptin, through the selective inhibition of DPP4, enhances glucose-mediated insulin secretion (incretin effect). Dapagliflozin, a selective inhibitor of SGLT2, inhibits renal glucose reabsorption independently of insulin. Actions of both drugs are regulated by the plasma glucose level.

Saxagliptin: Saxagliptin is a potent, selective, reversible, competitive, DPP4 inhibitor. Saxagliptin demonstrates selectivity for DPP4 versus other DPP enzymes, including DPP8 and DPP9. Saxagliptin has extended binding to the DPP4 active site, prolonging its inhibition of DPP4. Saxagliptin exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones, including GLP-1. The concentration of active (intact) GLP-1 incretin hormone is increased.

Incretin hormones are released by the intestine throughout the day and concentrations are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production.

The concentration of GLP-1 is reduced in patients with type 2 diabetes, but saxagliptin increases active GLP-1 concentration. By increasing active GLP-1 concentration, saxagliptin increases postprandial insulin release and decreases postprandial glucagon concentrations in the circulation in a glucose-dependent manner. In patients with type 2 diabetes with

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hyperglycemia, these changes in insulin and glucagon levels may lead to lower HbA1c and lower fasting and postprandial glucose concentrations.

Dapagliflozin: Dapagliflozin is a reversible inhibitor of SGLT2 that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis).

SGLT2 is selectively expressed in the kidney. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycemia. Dapagliflozin acts independently of insulin secretion and insulin action.

Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis.

Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is greater than 1400 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

Pharmacodynamics

Saxagliptin: In patients with type 2 diabetes, administration of saxagliptin led to dose-dependent inhibition of DPP4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1, decreased postprandial glucagon concentrations, and increased glucose-dependent beta cell responsiveness with higher postprandial insulin and C-peptide concentrations. 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.

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. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in patients with type 2 diabetes mellitus for 12 weeks. This glucose elimination rate approached the maximum glucose excretion observed at 20 mg/day of dapagliflozin. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume. Urinary volume increases in patients with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375

mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from 18.3 to 48.3 μmol/L (0.33 mg/dL to 0.87 mg/dL).

Cardiac Electrophysiology

Saxagliptin: In a randomized, double-blind, placebo-controlled, 4-way crossover, active comparator study, 40 healthy subjects were administered saxagliptin 40 mg (8 times the RHD), saxagliptin 10 mg (2 times the RHD), or placebo once daily for 4 days, or a single dose of moxifloxacin 400 mg as a positive control. The saxagliptin 10 mg and 40 mg treatments were not associated with any prolongation of the QTc, QRS, or PR intervals. In the saxagliptin 10 mg treatment a significant increase in heart rate was observed at 0.5, 1, 1.5, 4, and 12 h post-dosing, with a maximum placebo- and baseline-corrected mean increase of 3.75 (90% 1.55, 5.95) beats per minute at 0.5 post-dosing when the baseline-corrected change in the placebo treatment at this time was -1.4 (90% CI -3.0, 0.1) beats per minute. Significant increases in heart rate were also observed in the saxagliptin 40 mg treatment at 0.5, 4, and 12 hours post-dosing, with a maximum placebo- and baseline-corrected mean increase of 4.5 (90% CI 2.23, 6.82) beats per minute at 4 hours post-dose dose when the baseline-corrected change in the placebo treatment at this time was -3.3 (90% CI -5.0, -1.6) beats per minute. The effect of the recommended 5 mg dose was not investigated in this study.

Dapagliflozin: In a double-blind, randomized, placebo- and positive-controlled crossover study, single oral doses of dapagliflozin 20 mg and 150 mg were not associated with clinically or statistically significant effects on the QTc interval, the QRS duration, the PR interval, or heart rate in healthy subjects (n=36).

Pharmacokinetics

Absorption:

In a randomized, cross-over comparative bioavailability study in adult subjects, QTERN (saxagliptin/dapagliflozin) 2.5 mg/5 mg and 5 mg/10 mg fixed dose combination tablets were administered as single doses to healthy volunteers in fasted conditions. Their bioavailability was compared to that of individual saxagliptin (2.5 or 5 mg) and dapagliflozin (5 or 10 mg) tablets administered together. The bioavailability of both the saxagliptin and dapagliflozin components of QTERN tablets was comparable to their respective individual components administered together.

Table 9 **Geometric mean pharmacokinetic parameters for saxagliptin and dapagliflozin following single oral dose of QTERN or coadministration of corresponding doses of saxagliptin and dapagliflozin as individual tablets to healthy subjects under fasted and fed conditions**

Treatment	N	$AUC_{(0-t)}$ (ng*h/mL)	$AUC_{(INF)}$ (ng*h/mL)	C_{max} (ng/mL)
Saxagliptin				
A	36	47.8	49.1	12.8
B	36	49.7	51.1	13.4
C	36	58.4	59.7	12.6
D	35	95.6	97.2	26.1
E	35	96.4	97.5	27.6
F	36	111	113	25.6
Dapagliflozin				
A	36	313	321	78.5
B	36	314	323	85.6
C	36	293	303	45.1
D	35	580	598	150
E	35	601	620	141
F	36	557	582	91.3

Treatment A: 2.5-mg saxagliptin + 5-mg dapagliflozin tablets under fasted conditions
Treatment B: 2.5-mg saxagliptin/5-mg dapagliflozin FDC tablet under fasted conditions
Treatment C: 2.5-mg saxagliptin/5-mg dapagliflozin FDC tablet under fed conditions
Treatment D: 5-mg saxagliptin + 10-mg dapagliflozin tablets under fasted conditions
Treatment E: 5-mg saxagliptin/10-mg dapagliflozin FDC tablet under fasted conditions
Treatment F: 5-mg saxagliptin/10-mg dapagliflozin FDC tablet under fed conditions

The effects of food on the pharmacokinetics of both the saxagliptin and dapagliflozin from QTERN were similar to those previously observed for the individual components. Administration of QTERN with a high-fat meal decreased dapagliflozin C_{max} by up to 35% and prolonged T_{max} by approximately 1.5 hours, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful. There was no food effect observed for saxagliptin. QTERN can be administered with or without food.

Saxagliptin: The pharmacokinetics of saxagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes.

Saxagliptin was rapidly absorbed after oral administration, with an oral bioavailability of at least 75%. Maximum saxagliptin plasma concentrations (C_{max}) were usually attained within two hours after administration in the fasted state. The C_{max} and AUC values increased proportionally to the increment in the saxagliptin dose.

Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC(INF) value for saxagliptin's major metabolite was 214 ng·h/mL. The corresponding plasma C_{max} value was 47 ng/mL.

Following a single oral dose of 5 mg saxagliptin to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin was 2.5 hours, and the mean $t_{1/2}$ value for plasma DPP4 inhibition was 26.9 hours. The inhibition of plasma DPP4 activity by saxagliptin occurs for at least 24-hours after oral administration of saxagliptin. No appreciable accumulation was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence was observed in the clearance of saxagliptin and its major metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 mg to 400 mg. Results from population-based exposure modeling suggest that the pharmacokinetics of saxagliptin and its major metabolite were similar in healthy subjects and in patients with type 2 diabetes.

Dapagliflozin: Dapagliflozin was rapidly and well absorbed after oral administration. Geometric mean steady-state dapagliflozin Cmax and AUCτ values following once daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ng.h/mL, respectively. Maximum dapagliflozin plasma concentrations (Cmax) were usually attained within 2 hours after administration in the fasted state. The Cmax and AUC values increased proportionally to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%.

Distribution:

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

Dapagliflozin: Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (eg, renal or hepatic impairment).

Metabolism:

Saxagliptin: The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a selective, reversible, competitive DPP4 inhibitor, half as potent as saxagliptin.

Dapagliflozin: Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. 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 [^{14}C]-dapagliflozin dose and was the predominant drug-related component in human plasma, accounting for 42% (based on $AUC_{[0-12\,h]}$) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounted for >5% of the total plasma radioactivity

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at any time point measured. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

Excretion:

Saxagliptin: Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its major 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. For the major metabolite, renal clearance values were comparable to estimated glomerular filtration rate. 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.

Dapagliflozin: Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin. After administration of 50 mg [^{14}C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in feces. In feces, approximately 15% of the dose was excreted as parent drug.

Pharmacokinetics of the Major Metabolite:

Saxagliptin: The C_{max} and AUC values for the major metabolite of saxagliptin increased proportionally to the increment in the saxagliptin dose. Following single oral doses of 2.5 mg to 400 mg saxagliptin in the fed or fasted states, the mean AUC values for the major metabolite ranged from 2- and 7 times higher than the parent saxagliptin exposures on a molar basis. Following a single oral dose of 5 mg saxagliptin in the fasted state, the mean terminal half-life ($t_{1/2}$) value for the major metabolite was 3.1 hours and no appreciable accumulation was observed upon repeated once-daily dosing at any dose.

Special Populations and Conditions

Pediatrics (<18 years of age): QTERN should not be used in pediatric patients. Pharmacokinetics in the pediatric population have not been studied.

Geriatrics (≥65 years of age): QTERN is not recommended in patients aged 75 years and older. Use QTERN with caution in patients aged 65 and older. Because elderly patients are more likely to have decreased renal function, care should be taken in the elderly (age ≥65 years) based on renal function.

Saxagliptin: Elderly subjects (65-80 years) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively, for parent saxagliptin than young subjects (18-40 years). Differences in major metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in parent saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the major metabolite in

young and elderly subjects is likely to be due to multiple factors including declining renal function and metabolic capacity with increasing age.

Dapagliflozin: The effect of age (young: ≥18 to <40 years [n=105] and elderly: ≥65 years [n=224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥40 to <65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10.4% lower than in the reference group (90% CI: 87.9, 92.2%) and 25% higher in elderly patients compared to the reference group (90% CI: 123, 129%).

Gender: QTERN may be used regardless of gender.

Saxagliptin: There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the major metabolite than males, but the clinical relevance of this difference is unknown.

Dapagliflozin: Gender was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. The mean dapagliflozin AUCss in females (n=619) was estimated to be 22% higher than in males (n=634) (90% CI: 117,124).

Race: QTERN may be used regardless of race.

Saxagliptin: An exposure modeling analysis compared the pharmacokinetics of saxagliptin and its major metabolite in 309 white subjects with 105 non-white subjects (consisting of 6 race groups). No significant difference in the pharmacokinetics of saxagliptin and its major metabolite were detected between these two populations.

Dapagliflozin: Race (white, black or Asian) was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. Differences in systemic exposures between these races were small. Compared to whites (n=1147), Asian subjects (n=47) had no difference in estimated mean dapagliflozin systemic exposures (90% CI range 3.7% lower, 1% higher). Compared to whites, black subjects (n=43) had 4.9% lower estimated mean dapagliflozin systemic exposures (90% CI range 7.7% lower, 3.7% lower).

Body Mass Index: There is no restriction on the use of QTERN based on body mass index (BMI).

Dapagliflozin: In a population pharmacokinetic analysis using data from healthy subject and patient studies, systemic exposures in high body weight subjects (≥120 kg, n=91) were estimated to be 78.3% (90% CI: 78.2, 83.2%) of those of reference subjects with body weight between 75 and 100 kg. No dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with high body weight (≥120 kg) is recommended.

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Subjects with low body weights (<50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozin systemic exposures were simulated with a large number of subjects. The simulated mean dapagliflozin systemic exposures in low body weight subjects were estimated to be 29% higher than subjects with the reference group body weight. Based on these findings no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with low body weight (<50 kg) is recommended.

Hepatic Impairment:

QTERN is not recommended for use in patients with moderate to severe hepatic impairment.

Saxagliptin: In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean C_{max} and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin. The corresponding C_{max} and AUC of the major metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls.

Dapagliflozin: A single dose (10 mg) dapagliflozin clinical pharmacology study was conducted in patients with mild, moderate or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls. There were no differences in the protein binding of dapagliflozin between patients with hepatic impairment compared to healthy subjects. In patients with mild or moderate hepatic impairment mean Cmax and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. In patients with severe hepatic impairment (Child-Pugh class C) mean Cmax and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively.

Renal Insufficiency: QTERN is contraindicated in patients with moderate to severe renal impairment (eGFR <60 mL/min/1.73 m^2). QTERN should be discontinued when eGFR is <60 mL/min/1.73m^2 (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Saxagliptin: A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects (n=8 in each group) with varying degrees of chronic renal impairment compared to subjects with normal renal function. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (>50 to ≤80 mL/min), moderate (30 to ≤50 mL/min), and severe (<30 mL/min), as well as patients with ESRD on hemodialysis. Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault formula:

Males: $$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]}$$

Females: 0.85 x value calculated using formula for males

In subjects with mild renal impairment, the AUC values of saxagliptin and its major metabolite were 1.2- and 1.7-fold higher, respectively, than AUC values in subjects with normal renal function. Because increases of this magnitude are not clinically relevant, dosage adjustment in patients with mild renal impairment is not recommended.

In subjects with moderate or severe renal impairment or in subjects with ESRD on hemodialysis, the AUC values of saxagliptin and its major metabolite were up to 2.1- and 4.5-fold higher, respectively, than AUC values in subjects with normal renal function. The dose of saxagliptin should be reduced to 2.5 mg once daily in patients with moderate or severe renal impairment (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Dapagliflozin: Dapagliflozin is contraindicated in patients with moderate to severe renal impairment (eGFR <60 mL/min/1.73 m^2). Dapagliflozin should be discontinued when eGFR is <60 mL/min/1.73m^2 (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION). At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes and mild, moderate or severe renal impairment (as determined by iohexol clearance) had mean systemic exposures of dapagliflozin that were 32%, 60% and 87% higher, respectively, than those of patients with type 2 diabetes and normal renal function. Higher systemic exposures to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal glucose clearance or total cumulative glucose excretion. The renal glucose clearance and 24-hour glucose excretion were lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of hemodialysis on dapagliflozin exposure is not known.

STORAGE AND STABILITY

Store between 2-30°C.

Keep in a safe place out of reach of children.

SPECIAL HANDLING INSTRUCTIONS

No special requirements. Unused medication should not be disposed of down the drain or in household garbage.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

QTERN tablets containing 5 mg saxagliptin and 5 mg dapagliflozin are light purple to reddish purple, biconvex, round, film-coated tablets, with "5/5" printed on one side, and "1120" printed on the other side, in blue ink.

QTERN tablets containing 5 mg saxagliptin and 10 mg dapagliflozin are light brown to brown, biconvex, round, film-coated tablets, with "5/10" printed on one side, and "1122" printed on the other side, in blue ink.

The 5 mg/5 mg tablets are provided in blisters in cartons of 30.

The 5 mg/10 mg tablets are provided in blisters in cartons of 30.

Information for the patient is provided as a package insert in the QTERN packages.

Composition

Each film-coated tablet of QTERN contains 5 mg saxagliptin as saxagliptin hydrochloride and dapagliflozin propanediol monohydrate equivalent to 5 mg or 10 mg dapagliflozin. The following inactive ingredients include: anhydrous lactose, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, silicon dioxide, talc, titanium dioxide, black iron oxide (5 mg/5 mg only), red iron oxide, yellow iron oxide (5 mg/10 mg only).

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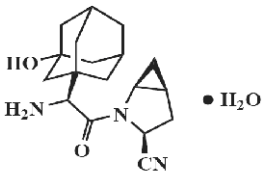
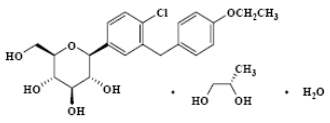
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	saxagliptin monohydrate[a]	dapagliflozin propanediol monohydrate
Chemical Name:	2-azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2*S*)-2-amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)acetyl]-, hydrate (1:1), (1*S*,3*S*,5*S*)- or (1*S*,3*S*,5*S*)-2-[(2*S*)-amino(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)acetyl]2-azabicyclo[3.1.0]hexane-3-carbonitrile monohydrate	D-glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1*S*)-,compd. with (2*S*)-1,2-propanediol, hydrate (1:1:1)
Molecular Formula and Molecular Mass:	$C_{18}H_{25}N_3O_2 \cdot H_2O$ 333.43; (315.41 anhydrous)	$C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$ 502.98; 408.87 (dapagliflozin)
Structural Formula:		
Physicochemical Properties:	Saxagliptin, in the free base monohydrate form, is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400).	Dapagliflozin propanediol is a white to off-white non-hygroscopic crystalline powder. It is slightly soluble in water, soluble in acetonitrile and freely soluble in acetone, ethanol, isopropanol, methanol and tetrahydrofuran.

[a] saxagliptin monohydrate is converted to saxagliptin hydrochloride *in-situ* during drug product manufacturing

CLINICAL TRIALS

Clinical efficacy and safety studies have not been conducted with QTERN (saxagliptin/dapagliflozin) tablets; however, bioequivalence of QTERN tablets with coadministered saxagliptin and dapagliflozin immediate release tablets was demonstrated (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

The efficacy and safety of the combination of saxagliptin 5 mg and dapagliflozin 10 mg was studied in three phase 3 randomized clinical trials. Indications for QTERN are supported by a single study discussed below.

The starting dose of dapagliflozin 5 mg was not evaluated in combination with saxagliptin.

Study demographics and trial design

Table 10 Summary of patient demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)*	Mean age (Range) †	Gender %M/%F†
Add-on therapy with dapagliflozin in patients inadequately controlled on saxagliptin plus metformin					
MB102129[1]	Randomized, double-blind, placebo-controlled, parallel-group, multicentre study	saxa 5 mg + dapa 10 mg + met (≥1500 mg) placebo + saxa 5 mg + met (≥1500 mg) Oral, 24 weeks (ST) 52 weeks (ST+LT)	(n = 160) (n = 160)	55.1 (30-75 years)	46/54

dapa=dapagliflozin, LT=long-term, met=metformin, saxa=saxagliptin, ST=short-term
* Number of subjects randomized
† Figures are at study start

Study results

Add-on therapy with dapagliflozin in patients inadequately controlled on saxagliptin plus metformin

A 24-week randomized, double-blind, placebo-controlled study was conducted with the sequential addition of 10 mg dapagliflozin to 5 mg saxagliptin and metformin compared to the addition of placebo to 5 mg saxagliptin (DDP4 inhibitor) and metformin in patients with inadequate glycemic control (HbA1c ≥ 7% and ≤ 10.5% at Week –2).

Following an open-label period where patients were maintained on stable metformin (≥1500 mg per day) and saxagliptin 5 mg therapy, 320 patients were randomized equally to receive either dapagliflozin 10 mg or placebo, each added on to the treatment background of saxagliptin + metformin for a 24-week double-blind treatment period. Patients who completed the initial 24-week study period were eligible to enter a controlled 28-week long-term study extension (52 weeks in total).

Approximately 16% of randomized patients were aged ≥65 years (one patient aged ≥75 years). Approximately 93% were White, and 6% were Black. The mean duration of diabetes was 7.6 years and the mean body mass index (BMI) was 32 kg/m^2.

The group with dapagliflozin sequentially added to saxagliptin + metformin achieved significantly (p-value <0.001) greater reductions in HbA1c versus the group with placebo sequentially added to saxagliptin + metformin at 24 weeks (see Table 11). The effect in HbA1c observed at Week 24 was sustained at Week 52.

Table 11 HbA1c change from baseline at Week 24 excluding data after rescue for randomized subjects in Study MB102129

Efficacy Parameter	**Dapagliflozin 10 mg added to Saxagliptin 5 mg + Metformin (N=160)** †	**Placebo + Saxagliptin 5 mg + Metformin (N=160)** †
HbA1c (%) at Week 24*		
Baseline (mean)	8.24	8.16
Change from baseline (adjusted mean‡)	−0.82	−0.10
Difference in HbA1c effect Adjusted mean‡ (95% CI) p-value	−0.72 (−0.91, −0.53) <0.001	

* LRM = Longitudinal repeated measures (using values prior to rescue).
† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.
‡ Least squares mean adjusted for baseline value.
dapa=dapagliflozin, met=metformin, saxa=saxagliptin

The proportion of patients achieving HbA1c <7.0% at Week 24 was 36.1% in the dapagliflozin + saxagliptin + metformin group compared to 11.6% in the placebo + saxagliptin + metformin group.

In the dapagliflozin add-on study, the adjusted mean changes from baseline at Week 24 in body weight were −1.91 kg in the dapagliflozin + saxagliptin + metformin group and −0.41 kg in the placebo + saxagliptin + metformin group. The mean difference (95% CI) between treatment groups was −1.50 kg (−2.12, −0.89).

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DETAILED PHARMACOLOGY

Saxagliptin: Saxagliptin and its major metabolite are potent reversible inhibitors of DPP4 *in vitro* with selectivity for DPP4 versus other enzymes, including other DPP family members such as DPP8 and DPP9. Saxagliptin and its major metabolite have extended binding to the DPP4 active site, prolonging their activity, but do not have extended duration of binding to other enzymes, including DPP8 and DPP9. Saxagliptin was a potent inhibitor of T-cell cell surface DPP activity in cell based assays, but did not inhibit T-cell activation either *in vitro* or *in vivo*.

Saxagliptin, when dosed orally, demonstrated dose-related inhibition of DPP4 in *ex vivo* assays in rats, dogs and cynomolgus monkeys. In acute *in vivo* studies, saxagliptin increased concentrations of intact GLP-1 in response to a meal in lean rats (maximum effect at 1 mg/kg). Saxagliptin also increased plasma insulin and lowered plasma glucose following an oral glucose tolerance test in obese insulin resistant and diabetic animal rodent models (maximum effect range 0.4 to 1.3 mg/kg). In chronic dosing studies using the progressively diabetic ZDF rat model, saxagliptin (4 mg/kg/day) delayed development of fasting hyperglycemia and the results of oral glucose tolerance tests showed significantly improved glucose homeostasis. These results are consistent with the mechanism of action of saxagliptin and its effects as an antihyperglycemic agent.

Dapagliflozin: The SGLT2 is selectively expressed in the kidney and is responsible for the majority of reabsorption of filtered glucose at that site. Dapagliflozin *in vitro* is a potent, competitive and reversible inhibitor of SGLT2. The Ki (inhibition constant) value for human SGLT2 is 0.2nM with selectivity vs. human SGLT1 of >3000-fold. Dapagliflozin is also highly selective for SGLT2 vs. the facilitative glucose transporters GLUT1, GLUT2 and GLUT4. The major human metabolite of dapagliflozin, dapagliflozin 3-O-glucuronide, is 2500-fold less active at SGLT2 and is not expected to have pharmacologic activity at clinical relevant doses. Oral administration of dapagliflozin to normal and diabetic animal models increases the excretion of glucose in the urine and increases urine volume. In diabetic animal models, dapagliflozin lowers plasma glucose and demonstrates positive effects on insulin sensitivity and preservation of beta-cell function.

TOXICOLOGY

Acute and repeat-dose toxicity

No animal studies have been conducted with QTERN (saxagliptin/dapagliflozin) to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with dapagliflozin and saxagliptin individually.

Saxagliptin: Saxagliptin was observed to be well tolerated at single doses up to 2000 mg/kg in mice and rats and 25 mg/kg in cynomolgus monkeys. In rodents, 4000 mg/kg resulted in transient decreases in body-weight gain and activity and/or lethality. In monkeys, overt toxicity and lethality were observed at 50 mg/kg.

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The potential toxicity of saxagliptin was evaluated in a number of repeat-dose studies in mice, rats, dogs and monkeys. Saxagliptin administered to rats for 6 months at doses of 2, 20 and 100 mg/kg/day was well tolerated, causing only at the high dose, minimal splenic lymphoid hyperplasia and pulmonary histiocytosis. The no-observed-adverse-effect-level (20 mg/kg/day) was 36 times (males) and 78 times (females) the human exposure based on the recommended human dose of 5 mg/day (RHD). In dogs, saxagliptin administered orally at 5 and 10 mg/kg/day for 12 months caused toxicity in the intestinal tract, as evidenced by bloody and mucoid feces. The no-observed-adverse-effect-level was 1 mg/kg/day, 4 times the RHD. In monkeys, major target organ changes included skin lesions (scabs, erosions, and ulceration), lymphoid hyperplasia (primarily spleen and bone marrow) and multi-tissue mononuclear-cell infiltrates. Skin healing during the dosing period was observed with recovery of both skin and microscopic changes following a drug-free recovery period. The AUCs at the no effect level for these changes were 1 to 3 times the RHD.

Dapagliflozin: Dapagliflozin demonstrated low acute toxicity. The minimum lethal doses of dapagliflozin following single oral administration were 750 mg/kg in rats and 3000 mg/kg in mice.

Dapagliflozin was well tolerated when given orally to rats for up to 6 months at doses of ≤25 mg/kg/day (up to 340× the human exposures (AUC) at the maximum recommended human dose (MRHD) of 10 mg/day resulting in AUC 0.465 µg.h/mL, and in dogs for up to 12 months at doses of ≤120 mg/kg/day (up to 3300× the MRHD). In rats, renal lesions (mainly cortical tubular dilatation, medullary tubular dilatation, degeneration, necrosis, mineralization, and reactive hyperplasia, and exacerbation of chronic progressive nephropathy), increased trabecular bone, and tissue mineralization (associated with increased serum calcium), were observed at high-exposure multiples (≥2100× the MRHD). Despite achieving exposure multiples of ≥3200× the human exposure at the MRHD, there was no dose-limiting or target organ toxicities identified in the 12-month dog study.

Carcinogenicity

Saxagliptin: Two-year carcinogenicity studies were conducted in mice and rats at oral doses of 50, 250, and 600 mg/kg/day and 25, 75, 150, and 300 mg/kg/day, respectively. Saxagliptin did not induce tumors in either mice or rats at the highest doses evaluated. The highest doses evaluated in mice were equivalent to approximately 900 (males) and 1210 (females) times the human exposure at the recommended human dose of 5 mg/day (RHD). In rats, AUC exposures were approximately 370 (males) and 2300 (females) times the RHD.

Dapagliflozin: Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were equivalent to AUC exposure multiples of approximately 72× (males) and 105× (females) the human AUC at the MRHD. In rats, AUC exposures were approximately 131× (males) and 186× (females) the human AUC at the MRHD.

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Mutagenesis

Saxagliptin: The mutagenic and clastogenic potential of saxagliptin was tested at high concentrations and exposures in a battery of genetic toxicity studies including an *in vitro* Ames bacterial assay, an *in vitro* cytogenetics assay in primary human lymphocytes, an *in vivo* oral micronucleus assay in rats, an *in vivo* oral DNA repair study in rats, and an oral *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes. Saxagliptin was not mutagenic or clastogenic based on the combined outcomes of these studies. The major metabolite was not mutagenic in an *in vitro* Ames bacterial assay.

Dapagliflozin: Dapagliflozin was negative in the Ames mutagenicity assay, and was positive in *in vitro* clastogenicity assays but only in the presence of S9 activation and at concentrations ≥100 μg/mL. Dapagliflozin was negative for clastogenicity *in vivo* in a series of studies evaluating micronuclei or DNA repair in rats at exposure multiples >2100× the human exposure at the MRHD. These studies, along with the absence of tumor findings in the rat and mouse carcinogenicity studies, support that dapagliflozin does not represent a genotoxic risk to humans.

Reproduction

Saxagliptin: In a rat fertility study, males were treated with oral gavage doses of 100, 200, and 400 mg/kg/day for two weeks prior to mating, during mating, and up to scheduled termination (approximately four weeks total) and females were treated with oral gavage doses of 125, 300, and 750 mg/kg/day for two weeks prior to mating through gestation day 7. No adverse effects on fertility were observed at 200 mg/kg/day (males) or 125 mg/kg/day (females) resulting in respective exposures (AUC) of approximately 630 (males) and 805 (females) times human exposure at the RHD. At higher, maternally toxic doses (300 and 750 mg/kg/day), increased fetal resorptions were observed (approximately 2150 and 6375 times the RHD). Additional effects on estrous cycling, fertility, ovulation, and implantation were observed at 750 mg/kg (approximately 6375 times the RHD).

Dapagliflozin: In a study of fertility and early embryonic development in rats, dapagliflozin had no effects on mating, fertility, or early embryonic development in treated males or females at exposure multiples up to 998× and 1708× the MHRD in males and females, respectively.

Development

Saxagliptin: Saxagliptin was not teratogenic at any dose evaluated in rats or rabbits. At high doses in rats, saxagliptin caused a minor and reversible developmental delay in ossification of the fetal pelvis at ≥240 mg/kg/day (≥1560 times the human exposure [AUC] at the RHD). Maternal toxicity and reduced fetal body weights were observed at 900 mg/kg/day (8290 times the RHD). In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (200 mg/kg/day, exposures 1420 times the RHD).

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Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (≥250 mg/kg/day, exposures ≥1690 times the RHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

Dapagliflozin: In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥15× the MRHD. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a pre- and postnatal development study, maternal rats were dosed from gestation day (GD) 6 through lactation day 21 at 1, 15, or 75 mg/kg/day, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415× and 137×, respectively, the human values at the MHRD). Dose-related reductions in pup body weights were observed at doses ≥15 mg/kg/day (pup exposures were ≥29× the human values at the MRHD). Maternal toxicity was evident only at 75 mg/kg/day, and limited to transient reductions in body weight and food consumption at dose initiation. The no-adverse-effect level (NOAEL) for developmental toxicity was 1 mg/kg/day (maternal exposure was 19× the human value at the MRHD).

In embryo-fetal development studies in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits up to the highest dose of 180 mg/kg/day (184× the MRHD). In rats, dapagliflozin was not teratogenic at doses up to 75 mg/kg/day (1441× the MRHD). Doses ≥150 mg/kg/day (≥2344× the MRHD) were associated with both maternal and developmental toxicities. Developmental toxicity consisted of reduced fetal body weights, increased embryo-fetal lethality, and increased incidences of fetal malformations and skeletal variations. Malformations included great vessel malformations, fused ribs and vertebral centras, and duplicated manubria and sternal centra. Variations were primarily reduced ossifications.

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REFERENCES

1. Mathieu C, Ranetti AE, Li D, Ekholm E, Cook W, Hirshberg B, et al. A randomized, double-blind, Phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes. Diabetes Care 2015; DOI: 10.2337/dc150779. [Epub ahead of print]

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr QTERN®

saxagliptin and dapagliflozin tablets
(as saxagliptin hydrochloride and dapagliflozin propanediol monohydrate)

Read this carefully before you start taking QTERN and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about QTERN.

Serious Warnings and Precautions

- **Diabetic ketoacidosis (DKA)**, is a serious and life-threatening condition that requires urgent hospitalization. DKA has been reported in patients with type 2 diabetes mellitus (T2DM) with normal or high blood sugar levels who are treated with dapagliflozin, one of the medicines in QTERN, and other sodium-glucose co-transporter 2 (SGLT2) inhibitors. Some cases of DKA have led to death.
- Seek medical attention right away and **stop taking QTERN immediately** if you have any of the following symptoms (even if your blood sugar levels are normal): difficulty breathing, nausea, vomiting, stomach pain, loss of appetite, confusion, feeling very thirsty, feeling unusually tired, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat.

Do not use QTERN if you have:

- DKA or a history of DKA
- type 1 diabetes.

What is QTERN used for?

QTERN is used with metformin, along with diet and exercise, to improve blood sugar levels in adults with type 2 diabetes who:

- are not controlled on metformin and saxagliptin (ONGLYZA®), or
- are currently treated with metformin, saxagliptin and dapagliflozin (FORXIGA®) as separate tablets.

QTERN replaces both dapagliflozin and saxagliptin. If you are already taking saxagliptin and / or dapagliflozin as separate tablets, **you must stop taking these drugs when you start QTERN**.

How does QTERN work?

QTERN contains saxagliptin and dapagliflozin. Saxagliptin belongs to a class of medicines called DPP4 inhibitors (dipeptidyl peptidase 4 inhibitors). Dapagliflozin belongs to a class of medicines called SGLT2 inhibitors (sodium-glucose co-transporter 2 inhibitors).

Saxagliptin lowers blood sugar levels after a meal. It also lowers blood sugar levels between meals and decreases the amount of sugar made by your body.
Dapagliflozin removes excess sugar from the body and passes it through your urine.

What are the ingredients in QTERN?
Medicinal ingredients: saxagliptin (as saxagliptin hydrochloride) and dapagliflozin (as dapagliflozin propanediol monohydrate)
Non-medicinal ingredients: anhydrous lactose, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, silicon dioxide, talc, titanium dioxide, black iron oxide (5 mg/5 mg only), red iron oxide, yellow iron oxide (5 mg/10 mg only)

QTERN comes in the following dosage forms:
As tablets containing:
- 5 mg saxagliptin and 5 mg dapagliflozin or;
- 5 mg saxagliptin and 10 mg dapagliflozin.

Do not use QTERN if you:
- have type 1 diabetes;
- have or have had **diabetic ketoacidosis (DKA)**, diabetic pre-coma or diabetic coma;
- have moderate to severe kidney problems or you have end-stage renal disease (ESRD) that requires dialysis;
- have severe liver disease;
- have bladder cancer;
- take pioglitazone, a medicine used to lower your blood sugar level;
- are pregnant, or are planning to become pregnant;
- are breast-feeding, or are planning to breast feed;
- are under 18 years of age;
- are allergic to medicines in the DPP4 inhibitor class;
- are allergic to medicines in the SGLT2 inhibitor class;
- are allergic to any of the ingredients in QTERN.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take QTERN. Talk about any health conditions or problems you may have, including if you:
- have an increased chance of developing **diabetic ketoacidosis (DKA)**, including if you:
  - are dehydrated or suffer from excessive vomiting, diarrhea, or sweating
  - are on a very low carbohydrate diet
  - drink a lot of alcohol
  - have/have had problems with your pancreas, including pancreatitis or surgery on your pancreas
  - are hospitalized for major surgery, serious infection or serious medical illness
  - have a history of diabetic ketoacidosis (DKA);

- are 65 years of age or older. The use of QTERN is not recommended in patients who are older than 75 year of age;
- have or have had any kidney problems;
- have heart disease;
- have low blood pressure;
- have or have had heart failure;
- have or have had problems with your pancreas, including inflammation of the pancreas, known as pancreatitis;
- are or get dehydrated. Or, if you have excessive vomiting, diarrhea or sweating. Or, if you are not able to eat or drink;
- are taking a medicine to lower your blood pressure;
- are taking a diuretic, known as a water pill. Diuretics are used to remove excess water from the body;
- are taking other medicines to lower your blood sugar. Tell your doctor about all of the medicines you are taking to control your diabetes;
- have a history of bladder cancer;
- have or have had liver problems;
- have been told by a doctor that you have a reduced immune system. For example if you have had organ transplantation. Or if you have human immunodeficiency virus infection / acquired immune deficiency syndrome (HIV/AIDS);
- have a history of yeast infections of the vagina or penis. QTERN increases your chance of getting a yeast infection of the penis or vagina and this is more likely if you have had a yeast infection in the past;
- get urinary tract infections often.

Other warnings you should know about:

Saxagliptin, one of the medicines in QTERN may increase risk for Heart Failure. Heart Failure is when your heart is unable to pump enough blood to meet the needs of the body. You are at greater risk of Heart Failure if you have or have had:

- heart or blood vessel disease including heart failure and heart attack
- kidney disease
- several risk factors of getting heart disease

Symptoms of heart failure include one or more of the following: tiredness, swollen ankles, a fast increase in weight and increased shortness of breath especially when lying down. This is serious. Stop taking QTERN and get immediate medical help if this happens to you.

Your blood sugar may get too high (hyperglycemia) if you have fever, infection, surgery, or trauma (stress conditions). In such cases contact your doctor as your medication may need to be adjusted.

QTERN may cause dizziness or light-headedness. Do not drive or use machines until you know how the medicine affects you.

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QTERN may cause changes in the amount of cholesterol or fats in your blood.

QTERN may cause abnormal kidney function. Your doctor will do blood tests to monitor how well your kidneys are working while you are taking QTERN.

QTERN contains lactose. Do not take QTERN if a doctor has told you that you have one of the following hereditary diseases: galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with QTERN:

- some medicines you take for diabetes to lower your blood sugar levels;
- medicines used to treat seizures such as carbamazepine, phenytoin or phenobarbital may require that your doctor monitor control of your blood sugar levels more closely;
- rifampin (used to treat bacterial infections), or dexamethazone (a steroid) may require that your doctor monitor control of your blood sugar levels more closely;
- medicines used to lower your blood pressure;
- diuretics, known as water pills, such as furosemide. They are used to remove excess water from the body;
- ketoconazole if taken by mouth, used to treat fungal infections;
- an herbal medicine called St. John's wort.

How to take QTERN:

Follow the directions given to you by your doctor.

Take QTERN:

- once a day
- at any time of the day, at around the same time each day
- by mouth
- with or without food

Swallow whole. Do not cut or divide tablets.

Diet and exercise can help your body control its blood sugar better. It is important to stay on the diet and exercise program recommended by your doctor while taking QTERN.

Usual dose:

The recommended starting dose of QTERN is one 5 mg/5 mg tablet taken once a day. In some patients the dose may be increased to one 5 mg/10 mg tablet taken once a day. Your doctor will tell you which dose of QTERN to take.

Overdose:

If you think you, or a person you are caring for, have taken too much QTERN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you forget to take a dose of QTERN, take it as soon as you remember. If you do not remember until it is almost time for your next dose, skip the missed dose.
- Never take two doses of QTERN at the same time.

What are possible side effects from using QTERN?
These are not all the possible side effects you may feel when taking QTERN. If you experience any side effects not listed here, contact your healthcare professional. Please also see the **Serious Warnings and Precautions** box.

Side effects may include:

- common cold (sore throat, stuffy and / or runny nose)
- cough (with or without phlegm)
- flu (fever, tiredness, body aches)
- diarrhea
- nausea and vomiting
- abdominal pain
- constipation
- dry mouth
- passing more urine than usual or needing to pass urine more often
- back pain
- joint paint (pain in the arms, legs, hands or feet)
- headache and / or dizziness
- weight loss
- rash

If any of these affects you severely, tell your doctor or pharmacist.

Diabetic ketoacidosis (DKA) is a serious medical condition normally seen at high blood sugar levels; however, it has also been seen at near normal blood sugar levels. Get medical help right away if you have any of the symptoms in the table below under **Diabetic ketoacidosis (DKA)** even if your blood sugar levels are normal.

Your doctor will tell you what to do if you get any of the symptoms of low blood sugar. Symptoms of low blood sugar include shaking, sweating, fast heartbeat, change in vision, hunger, headache and a change in mood. If you have symptoms of low blood sugar, eat glucose tablets, a high sugar snack or drink fruit juice and then talk to your healthcare professional.

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QTERN can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results. They may check kidney function, blood fat levels (Low Density Lipoprotein cholesterol or LDL-C) and amount of red blood cells in your blood (hematocrit).

QTERN will cause your urine to test positive for sugar (glucose). This is expected when you take QTERN.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Urinary tract infection: difficulty or increased need to urinate; pain or burning sensation when passing urine; urine that appears cloudy; pain in the pelvis; or mid-back pain.		X	
Yeast infection of vagina: itching, burning, pain, soreness, redness, swelling or irritation of the vagina or vulva; a thick, white vaginal discharge with a cottage cheese appearance.	X		
Yeast infection of penis: redness, swelling, itching, irritation or soreness of the head of the penis; thick, lumpy discharge under foreskin with an unpleasant odour; difficulty pulling back the foreskin; pain passing urine or during sex.	X		
UNCOMMON			
Pancreatitis (inflammation of the pancreas): prolonged severe abdominal pain which may be accompanied by vomiting; pain may spread out towards the back.		X	X
Severe disabling joint pain		X	
Volume depletion (loss of needed fluids from the body; dehydration): dry or sticky mouth; headache; dizziness; urinating less often than normal.		X	

Low blood pressure: dizziness, light-headedness, or fainting which may occur when you go from lying down to sitting or standing up.		X	
Low blood sugar (hypoglycemia): shaking; sweating; rapid heartbeat; change in vision; hunger; headache; change in mood.		X	
RARE			
Diabetic ketoacidosis (DKA): difficulty breathing; nausea; vomiting; stomach pain; loss of appetite; confusion; feeling very thirsty; feeling unusually tired; a sweet smell to the breath; a sweet or metallic taste in the mouth; a different odour to urine or sweat.			X
Kidney problems: any change in the amount, frequency or colour (pale or dark) of urine.		X	
VERY RARE			
Allergic (hypersensitivity) reaction: rash; hives; swelling of face, lips or throat that may cause difficulty in breathing or swallowing.		X	X
Bullous pemphigoid (serious skin reaction): blistering of the skin, redness, peeling skin.		X	
Acute kidney infection: painful, urgent or frequent urination; pain in the lower back on either side; fever or chills; cloudy or foul smelling urine; blood in urine.			X
Severe infection that spreads from urinary tract throughout body (sepsis): fever or low body temperature; chills; rapid breathing; rapid heartbeat; pain with urination; difficulty urinating; frequent urination.			X

Thrombocytopenia (low levels of blood platelets): easy or excessive bruising; tiny red dots on skin; prolonged bleeding from cuts; bleeding from gums or nose; blood in urine or stool; fatigue and weakness.		X	
Rhabdomyolysis (breakdown of damaged muscle): muscle spasms, weakness, red-brown (tea-coloured) urine			X
UNKNOWN			
Heart failure (a weakness of the heart): tiredness; swollen ankles; increasing shortness of breath especially when lying down; a fast increase in weight.			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- By calling 1-866-234-2345 (toll-free).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 2-30°C.

Keep out of reach and sight of children.

If you want more information about QTERN:

- Talk to your healthcare professional
- Find the full current product monograph that is prepared for healthcare professionals and includes the current Patient Medication Information by visiting the Health Canada website; the sponsor's website www.astrazeneca.ca, or by contacting the sponsor, AstraZeneca Canada Inc. at:

  Questions or concerns: 1-800-668-6000

NOTE: The PATIENT MEDICATION INFORMATION leaflet provides you with the most current information at the time of printing.

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