AUSTRALIAN PRODUCT INFORMATION

QTERN® 5/10
(SAXAGLIPTIN/DAPAGLIFLOZIN) TABLETS

1 NAME OF THE MEDICINE

Saxagliptin (as hydrochloride) /dapagliflozin propanediol monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

QTERN 5/10 is available as a film-coated tablet containing 5 mg saxagliptin as saxagliptin hydrochloride and dapagliflozin propanediol monohydrate equivalent to 10 mg dapagliflozin.

Excipient (s) with known effect: lactose

For the full list of excipients, see Section 6.1 List of Excipients

3 PHARMACEUTICAL FORM

Tablets.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

QTERN is indicated as an adjunct to diet and exercise, in combination with metformin, to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and dapagliflozin is appropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose of QTERN is one saxagliptin 5 mg/dapagliflozin10 mg tablet taken once daily at any time of the day, with or without food. Tablet is to be swallowed whole.

Please refer to Section 4.4 Special Warnings and Precautions for Use for information regarding combinations not studied.

Optimal medical management of patients with diabetes also involves attention to diet, exercise, blood glucose monitoring, assessment of complications and co-morbidities. Regular assessment and review of the compliance and benefit/risk of all therapies is recommended.

Special populations

Patients with renal impairment

Assess renal function prior to initiation of QTERN and periodically thereafter. No dose adjustment is required for patients with eGFR ≥45 mL/min/1.73 m^2.

The glycaemic efficacy of dapagliflozin is dependent on renal function. QTERN should not be used in patients with an estimated glomerular filtration rate (eGFR) persistently <45 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease [MDRD] formula or in patients with end-

stage renal disease (ESRD) or patients on dialysis (see Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Adverse Effects (Undesirable Effects)).

Patients with hepatic Impairment

QTERN may be used in patients with mild or moderate hepatic impairment. QTERN should not be used in patients with severe hepatic impairment (see Section 4.4 Special Warnings and Precautions for Use).

Paediatric and adolescent patients

Safety and effectiveness of QTERN in paediatric and adolescent patients (<18 years of age) have not been established.

Elderly patients

In general, no dosage adjustment is recommended based on age. Caution should be exercised due to the risk of hypovolaemia. Because elderly patients are more likely to have decreased renal function, care should be taken in the elderly based on renal function. (see Section 4.4 Special Warnings and Precautions for Use and Section 5 Pharmacological Properties).

Patients at risk for volume depletion

In patients with volume depletion, correcting this condition prior to initiation of QTERN is recommended (see Section 4.4 Special Warnings and Precautions for Use).

4.3 CONTRAINDICATIONS

- Hypersensitivity: QTERN is contraindicated in patients with a history of any serious hypersensitivity reaction to the active substances or to any of the excipients, including anaphylaxis or angioedema following exposure to any dipeptidyl peptidase-4 (DPP4) inhibitor or any sodium glucose cotransporter 2 (SGLT2) inhibitor.
- The glycaemic efficacy of dapagliflozin is dependent on renal function (see Section 4.4 Special Warnings and Precautions for Use). QTERN should not be used in patients with eGFR persistently <45 mL/min/1.73m^2 or patients on dialysis. (see Section 4.4 Special Warnings and Precautions for Use)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

QTERN should not be used in patients with type 1 diabetes (see Section 4.1 Therapeutic Indications) or for the treatment of diabetic ketoacidosis (see Section 4.4 Special Warnings and Precautions for Use – Ketoacidosis).

Use in renal impairment

Dapagliflozin increases serum creatinine and decreases eGFR (see Section 4.8 Adverse Effects (Undesirable Effects)). Renal function abnormalities can occur after initiating dapagliflozin. Patients with hypovolaemia may be more susceptible to these changes.

There have been post-marketing reports of acute kidney injury, some requiring hospitalisation and dialysis, in patients receiving SGLT2 inhibitors, including dapagliflozin; some reports involved patients younger than 65 years of age.

Monitoring of renal function is recommended as follows:

- prior to initiation of QTERN and at least yearly thereafter;
- prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter;

- for renal function where eGFR is between 45 and 60 mL/min/1.73 m^2, at least 2 to 4 times per year. If renal function falls persistently below eGFR <45 mL/min/1.73 m^2, treatment with QTERN should be discontinued (see Section 4.3 Contraindications).
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Use in hepatic impairment

Dapagliflozin exposure is increased in patients with severe hepatic impairment. Due to limited clinical experience in patients with hepatic impairment, QTERN should not be used in patients with severe hepatic impairment (see Section 4.2 Dose and Method of Administration and Section 5 Pharmacological Properties).

Use in patients at risk for volume depletion and or hypotension

The diuretic effect of dapagliflozin is a potential concern for volume depleted patients. Due to its mechanism of action, dapagliflozin induces osmotic diuresis which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1 Pharmacodynamic properties – Clinical trials).

When considering initiating QTERN, there may be patients for whom the additional diuretic effect of dapagliflozin is a potential concern either due to acute illness (such as gastrointestinal illness) or a history of hypotension or dehydration with diuretic therapy for patients who may become volume depleted. Initiation of therapy with QTERN is therefore not recommended in these patients.

In case of intercurrent conditions that may lead to volume depletion, such as gastrointestinal illness, heat stress or severe infections, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including electrolytes is recommended). Temporary interruption of QTERN is recommended for patients who develop volume depletion until the depletion is corrected (see Section 4.8 Adverse Effects (Undesirable Effects)).

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on antihypertensive therapy with a history of hypotension or elderly patients.

Use with medications known to cause hypoglycaemia

Both saxagliptin and dapagliflozin can individually increase the risk of hypoglycaemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycaemia if used in combination with QTERN (see Section 4.8 Adverse Effects (Undesirable Effects)).

Hypersensitivity reactions

During postmarketing experience the following adverse reactions have been reported with use of saxagliptin: serious hypersensitivity reactions, including anaphylaxis and angioedema. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency. If a serious hypersensitivity reaction to saxagliptin is suspected, discontinue QTERN, assess for other potential causes for the event, and institute alternative treatment for diabetes. (See Section 4.3 Contraindications and Section 4.8 Adverse Effects (Undesirable Effects.)

Pancreatitis

During postmarketing experience with saxagliptin, there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute

pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, QTERN should be discontinued. (See Section 4.8 Adverse Effects (Undesirable Effects))

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, the incidence of adjudicated pancreatitis events was 0.3% in both saxagliptin-treated patients and placebo-treated patients in the intent-to-treat population. (See 4.8 Section Adverse Effects (Undesirable Effects))

Ketoacidosis

QTERN should not be used for the treatment of diabetic ketoacidosis (DKA).

There have been reports of ketoacidosis, including DKA, a serious life-threatening condition requiring urgent hospitalisation, in patients taking dapagliflozin and other SGLT2 inhibitors. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin.

Patients treated with QTERN who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, QTERN should be suspended, the patient should be evaluated and prompt treatment initiated.

Treatment of ketoacidosis generally requires insulin, fluid, potassium and carbohydrate replacement.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended unless another clear precipitating factor is identified and resolved.

Before initiating QTERN, consider factors in the patient history that may predispose to ketoacidosis

Factors that predispose patients to ketoacidosis include insulin deficiency from any cause (including insulin pump failure, history of pancreatitis or pancreatic surgery), insulin dose reduction, reduced caloric intake or increased insulin requirements due to infections, low carbohydrate diet, acute illness, surgery, a previous ketoacidosis, dehydration and alcohol abuse. QTERN should be used with caution in these patients. Consider monitoring patients for ketoacidosis and temporarily discontinuing QTERN in clinical situations known to predispose to ketoacidosis.

Surgery

Treatment with QTERN should be ceased prior to major surgery. An increase in other glucose lowering agents may be required during this time. Patients scheduled for non-urgent surgery who have not ceased dapagliflozin should be assessed and consideration should be given to postponing the procedure.

Treatment with QTERN may be restarted once the patient’s condition has stabilised and oral intake is normal.

Urinary tract infections

There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving SGLT2 inhibitors, including dapagliflozin. Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to control in a placebo-pooled analysis up to 24 weeks (4.7% vs. 3.5%, respectively). Urinary glucose excretion may be associated with an increased risk of urinary tract infection. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated

(see Section 4.8 Adverse Effects (Undesirable Effects)). Temporary interruption of QTERN should be considered when treating pyelonephritis or urosepsis. Discontinuation of QTERN may be considered in cases of recurrent urinary tract infections; see Section 4.8 Adverse Effects (Undesirable Effects).

Necrotising fasciitis of the perineum (Fournier's gangrene)

Postmarketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and potentially life-threatening necrotising infection, have been reported in female and male patients with diabetes mellitus treated with SGLT2 inhibitors, including dapagliflozin [see section 4.8 Adverse effects (Undesirable effects)]. Serious outcomes have included hospitalisation, multiple surgeries, and death.

Patients treated with QTERN who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotising fasciitis. If suspected, QTERN should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Skin disorders

Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non-clinical toxicology studies with saxagliptin. Although skin lesions were not observed at an increased incidence in clinical trials, there is limited experience in patients with diabetic skin complications. Postmarketing reports of rash have been described in the DPP4 inhibitor class. Rash is also noted as an adverse event for saxagliptin (see Section 4.8 Adverse Effects (Undesirable Effects)). Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering, ulceration or rash, is recommended.

Bullous pemphigoid

Post-marketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving QTERN. If bullous pemphigoid is suspected, QTERN should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment (see Section 4.8 Adverse Effects (Undesirable Effects)).

Cardiac failure

Saxagliptin

Experience in NYHA class III-IV is still limited. In the SAVOR trial a small increase in the rate for hospitalisation for heart failure was observed in the saxagliptin treated patients compared to placebo, although a causal relationship has not been established. Additional analysis did not indicate a differential effect among NYHA classes. (See Section 4.8 Adverse Effects (Undesirable Effects) – Cardiovascular safety). Caution is warranted if QTERN is used in patients who have known risk factors for hospitalisation for heart failure or moderate to severe renal impairment. Patients should be advised of the characteristic symptoms of heart failure, and to immediately report such symptoms.

Dapagliflozin

There is limited clinical experience in clinical studies with dapagliflozin inpatients with NYHA class IV.

Arthralgia

Joint pain, which may be severe, has been reported in postmarketing reports for DPP4 inhibitors. Patients experienced relief of symptoms after discontinuation of the medication and some experienced recurrence of symptoms with reintroduction of the same or another DPP4 inhibitor. Onset of symptoms following initiation of drug therapy may be rapid or may occur after longer periods of treatment. If a patient presents with severe joint pain, continuation of drug therapy should be individually assessed. (See Section 4.8 Adverse Effects (Undesirable Effects)).

Combinations not studied

QTERN has not been studied in combination with glucagon like peptide 1 (GLP-1) analogues, insulin and insulin secretagogues, such as sulfonylureas.

Immunocompromised patients

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

Lower limb amputations

Dapagliflozin

In one long-term clinical study with another SGLT2 inhibitor, an increase in cases of lower limb amputation (primarily of the toe) has been observed. The medicine in that study is not dapagliflozin. However, it is unknown whether this constitutes a class effect. It is important to regularly examine the feet and counsel all patients with diabetes on routine preventative footcare.

Use in the elderly

Saxagliptin

Saxagliptin and its major metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in the elderly based on renal function. (See Sections 4.2 Dose and Method of Administration)

Dapagliflozin

No dosage adjustment for dapagliflozin is required based on age (see Section 4.2 Dose and administration). Older patients may be at greater risk of volume depletion and are more likely to have impaired renal function. The renal function recommendations provided for all patients also apply to elderly patients (see Section 4.4 Special Warnings and Precautions for Use).

Paediatric use

Safety and effectiveness of QTERN in paediatric patients have not been established. Delayed growth and metabolic acidosis in rats were observed in both sexes at higher doses of dapagliflozin (greater than or equal to 15 mg/kg/day). The developmental age of animals in this study approximately correlates to 2 to 16 years in humans.

Effects on laboratory tests

Saxagliptin

Across clinical studies, the incidence of laboratory adverse events was similar in patients treated with saxagliptin 5 mg alone or in combination compared to patients treated with placebo.

A small decrease in absolute lymphocyte count was observed. From a baseline mean absolute lymphocyte count of approximately 2.2 x 10^9 c/L, a mean decrease of approximately 0.1 x 10^9 c/L relative to placebo was observed in a pooled analysis of five placebo-controlled clinical studies. Mean absolute lymphocyte counts remained stable and within the normal limits with daily dosing up to 102 weeks in duration. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions.

In the SAVOR trial, decreased lymphocyte counts were reported in 0.5% of saxagliptin-treated patients and 0.4% of placebo-treated patients.

Dapagliflozin

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

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

Haematocrit

In the short-term placebo-controlled studies, at Week 24, marked laboratory abnormalities of increased haematocrit values >55% were reported at in 0.4% of placebo-treated patients and 1.3% of dapagliflozin 10 mg–treated patients. In placebo-controlled studies with long-term data, at Week 102, results for haematocrit values >55% were similar to Week 24. Most patients with marked abnormalities of elevated haematocrit or haemoglobin had elevations measured a single time that resolved at subsequent visits.

Serum Inorganic Phosphorus

In short-term placebo-controlled studies, higher proportions of patients with marked laboratory abnormalities of hyperphosphataemia were reported on dapagliflozin at Week-24 (0.9% versus 1.7% for placebo and dapagliflozin 10 mg, respectively).

In placebo-controlled studies with long-term data, at Week-102, hyperphosphataemia were reported in a higher proportion of patients in the dapagliflozin group compared to placebo (3.0% vs. 1.6%, respectively). The clinical relevance of these findings is unknown.

Lipids

Data from the saxagliptin and dapagliflozin plus metformin treatment arms of three Phase 3 trials, demonstrated trends of mean percent increases from baseline in total cholesterol, (ranging from 0.4% to 3.8%), LDL cholesterol (ranging from 2.1% to 6.9 %), and HDL cholesterol (ranging 2.3% to 5.2%) along with mean percent decreases from baseline in triglycerides (ranging from -3.0% to -10.8%).

Liver Function Tests

In the 21-study active and placebo-controlled pool (see Section 4.8 Adverse Effects (Undesirable Effects)), there was no imbalance across treatment groups in the incidence of elevations of ALT or AST. ALT >3 x ULN was reported in 1.2% of patients treated with dapagliflozin 10 mg and 1.6% treated with comparator. ALT or AST >3 x ULN and bilirubin >2 x ULN was reported in 0.1% of patients on any dose of dapagliflozin, 0.2% of patients on dapagliflozin 10 mg, and 0.1% of patients on comparator.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Saxagliptin and dapagliflozin

The lack of pharmacokinetic interaction between saxagliptin and dapagliflozin was demonstrated in a drug-drug interaction study between saxagliptin and dapagliflozin. No dose adjustment of either saxagliptin or dapagliflozin is needed when the two drugs are co administered *either separately or as the QTERN fixed-dose combination.*

See saxagliptin and dapagliflozin subsections for drug interactions. In summary, there are no clinically meaningful drug interactions expected for either saxagliptin or dapagliflozin or the QTERN fixed-dose combination.

Saxagliptin

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5) which converts it to an active metabolite. Therefore, drugs which inhibit the activity of this enzyme system may increase plasma concentrations of saxagliptin but reduce those of its metabolite, whereas CYP3A inducers will tend to do the opposite. However, the overall biological effect of saxagliptin is unaffected by coadministration with inhibitors or inducers of CYP3A4/5.

In *in vitro* studies, saxagliptin and its major metabolite neither inhibited CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or 3A4, nor inhibited UGT1A9. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolised by these enzymes. Saxagliptin is neither a significant inhibitor of P-glycoprotein (P-gp) nor an inducer of P-gp.

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.

In studies conducted in healthy subjects, the pharmacokinetics of saxagliptin, its major metabolite, were altered by some drugs which affect the CYP3A4/5 system. However, total exposure to the total active components of saxagliptin (parent+metabolite), were not meaningfully altered by metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole, rifampicin, omeprazole, aluminum hydroxide+magnesium hydroxide+simethicone combination, or famotidine. Saxagliptin also did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole or an estrogen/progestin combined oral contraceptive.

Other interactions

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

The safety and efficacy of saxagliptin in combination with alpha-glucosidase inhibitors or orlistat has not been established.

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 CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of coadministered drugs that are

metabolised by these enzymes, and drugs that inhibit or induce these enzymes are not expected to alter the metabolic clearance of dapagliflozin. 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.

In interaction studies conducted in healthy subjects, using mainly single dose design, the pharmacokinetics of dapagliflozin were not altered by metformin (an hOCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (an hOAT-3 substrate, and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), voglibose (an α-glucosidase inhibitor), hydrochlorothiazide, bumetanide, valsartan, simvastatin (a CYP3A4 substrate). Therefore, meaningful interaction of dapagliflozin with other substrates of hOCT-1, hOCT-2, hOAT-3, P-gp, CYP2C8, CYP2C9, CYP3A4, and other α-glucosidase inhibitors would not be expected.

Dapagliflozin also did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, simvastatin, digoxin (a P-gp substrate), or warfarin (S-warfarin is a CYP2C substrate). Therefore, dapagliflozin is not a clinical meaningful inhibitor of hOCT-1, hOCT-2, hOAT-3, P-gp transporter pathway, and CYP2C8, CYP2C9, CYP2C19 and CYP3A4 mediated metabolism.

Concomitant use of dapagliflozin and lithium may lead to a reduction in serum lithium concentrations due to a possible increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolizing enzymes) or mefenamic acid (an inhibitor of UGT1A9), a 22% decrease and a 51% increase, respectively, in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion in either case. No dose adjustment of dapagliflozin is recommended when dapagliflozin is coadministered with either rifampicin or mefenamic acid.

Other interactions

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies on the effect on fertility have been conducted with saxagliptin and dapagliflozin in combination.

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 670 (males) and 865 (females) times human exposure at the recommended clinical dose. At higher, maternally toxic doses (300 and 750 mg/kg/day), increased foetal resorptions were observed (approximately 2300 and 6810 times the recommended clinical dose). Additional effects

on oestrous cycling, fertility, ovulation, and implantation were observed at 750 mg/kg/day (approximately 6810 times the recommended clinical dose).

Dapagliflozin

In a study of fertility in rats, no effects on mating, fertility, or early embryonic development were seen when males received oral doses up to 210 mg/kg/day or when females received oral doses up to 75 mg/kg/day (yielding plasma AUC values at least 1000 times the clinical exposure at the maximum recommended human dose [MRHD] of 10 mg/day). However, at 210 mg/kg/day, a dose associated with profound toxicity (including mortality), seminal vesicle and epididymal weights were reduced; sperm motility and sperm counts were reduced; and there were increased numbers of morphologically abnormal sperm. No adverse effects on sperm or male reproductive organs were seen at 75 mg/kg/day (700 times the clinical exposure at the MRHD).

Use in pregnancy – Category D

Saxagliptin/dapagliflozin combination

There are no adequate and well-controlled studies of QTERN or its mono-components in pregnant women. Animal studies with the individual active components have identified adverse effects on embryofoetal development, most particularly with regard to dapagliflozin on the kidney. No animal developmental studies with saxagliptin and dapagliflozin in combination have been conducted. QTERN should not be used during pregnancy. If pregnancy is detected, treatment with QTERN should be discontinued.

Saxagliptin

Saxagliptin was not teratogenic at any dose evaluated in rats or rabbits. At high doses in rats, saxagliptin caused a minor developmental delay in ossification of the foetal pelvis at ≥240 mg/kg/day (≥1670 times the human exposure [AUC] at the recommended clinical dose). Maternal toxicity and reduced foetal body weights were observed at 900 mg/kg/day (>8860 times the recommended clinical dose). In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (200 mg/kg/day, exposures 1520 times the recommended clinical dose).

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 ≥1810 times the recommended clinical dose). No functional or behavioural toxicity was observed in the offspring of rats administered saxagliptin at any dose.

Saxagliptin and/or its metabolites cross the placenta into the foetus following dosing in pregnant rats.

Dapagliflozin

There are no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy (see Section 4.4 Special Warnings and Precautions for Use). Therefore, dapagliflozin must not be used during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with dapagliflozin should be discontinued.

In conventional studies of embryofoetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the period of organogenesis in humans. An increased incidence of embryofoetal lethality, decreased foetal weight and an increased incidence of foetal visceral and skeletal anomalies were seen in rats at maternotoxic doses (oral doses greater than or equal to 150 mg/kg/day). The no observed effect level for embryofoetal effects in rats was an oral dose of 75 mg/kg/day (1530 times the exposure in patients at the maximum recommended human

dose [MRHD]). No developmental toxicities were observed in rabbits at oral doses up to 180 mg/kg/day (1265 times the exposure in patients at the MRHD).

Use in lactation

Saxagliptin/dapagliflozin combination

It is not known whether QTERN or its mono-components and/or their metabolites are excreted in human milk. QTERN must not be used by a breastfeeding woman.

Saxagliptin

Saxagliptin and/or its metabolites are secreted in the milk of lactating rats.

Dapagliflozin

Studies in rats have shown excretion of dapagliflozin in milk. Direct and indirect exposure of dapagliflozin to weanling juvenile rats and during late pregnancy are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny, although the long-term functional consequences of these effects are unknown. These periods of exposure coincide with a critical window of renal maturation in rats. As functional maturation of the kidneys in humans continues in the first 2 years of life, dapagliflozin-associated dilated renal pelvis and tubules noted in juvenile rats could constitute 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that dizziness has been reported with saxagliptin. Patients should be alerted to the risk of hypoglycaemia when QTERN is used in combination with a sulphonylurea or insulin.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Significant adverse events are also described in the 4.4 Special Warnings and Precautions for Use section. The adverse events with QTERN are consistent with the adverse events for each component. For further information on adverse effects associated with the saxagliptin and dapagliflozin refer to the appropriate individual Product Information document.

Clinical trials

Saxagliptin/dapagliflozin fixed-dose combination has been demonstrated to be bioequivalent with co-administered saxagliptin and dapagliflozin. In therapeutic clinical trials, saxagliptin and dapagliflozin were administered as individual tablets.

The safety of combined use of 5 mg saxagliptin and 10 mg dapagliflozin has been evaluated in 1169 adult subjects with type 2 diabetes (T2DM) in an integrated safety pool of three phase 3 active/placebo controlled short-term and long-term clinical trials for up to 52 weeks. The median exposure for the saxagliptin and dapagliflozin plus metformin group was 359 days. At least 235 subjects in the saxagliptin and dapagliflozin plus metformin group received saxagliptin/dapagliflozin for >360 days. The pooled safety analysis is comprised of 3 treatment groups: saxagliptin and dapagliflozin plus metformin (492 subjects; data pooled from the concomitant therapy with saxagliptin and dapagliflozin study and the 2 sequential combination use studies); saxagliptin plus metformin (336 subjects data pooled from the concomitant therapy with saxagliptin and dapagliflozin and the dapagliflozin added to saxagliptin and metformin studies); and dapagliflozin plus metformin (341 subjects data pooled from the concomitant therapy with saxagliptin and dapagliflozin and the saxagliptin added to dapagliflozin and metformin studies).

The safety profile of the combined use of saxagliptin plus dapagliflozin in these trials was comparable to the individual monocomponents (see Table 1). The incidence of hypoglycaemia was low (1.4%). No episodes of major hypoglycaemia were reported, and no subject discontinued the study treatment due to hypoglycaemia.

Table 1 Common adverse events (reported in ≥2% of subjects in any treatment group) up to 52 weeks - Pooled Safety Analysis

Preferred term	Saxa + Dapa + Met N=492 (%)	Saxa + Met N=336 (%)	Dapa + Met N=341 (%)
Total subjects with an event	282 (57.3)	207 (61.6)	181 (53.1)
Infections and infestations			
Upper respiratory tract infection[*1]	67(13.6)	53 (15.8)	50 (14.7)
Urinary tract infection[*2]	28 (5.7)	25 (7.4)	19 (5.6)
Genital infection[*3]	15 (3.0)	3 (0.9)	20 (5.9)
Metabolism and nutrition disorders			
Dyslipidaemia[*4]	25 (5.1)	23 (6.8)	17 (5.0)
Hyperuricaemia	1 (0.2)	7 (2.1)	2 (0.6)
Nervous system disorders			
Headache	21 (4.3)	18 (5.4)	14 (4.1)
Gastrointestinal disorders			
Diarrhoea	18 (3.7)	12 (3.6)	8 (2.3)
Nausea	8 (1.6)	11 (3.3)	6 (1.8)
Dyspepsia	4 (0.8)	8 (2.4)	5 (1.5)
Musculoskeletal and connective tissue disorders			
Back pain	16 (3.3)	12 (3.6)	8 (2.3)
Arthralgia	12 (2.4)	4 (1.2)	3 (0.9)
Pain in extremity	5 (1.0)	7 (2.1)	6 (1.8)
Muscle spasms	3 (0.6)	7 (2.1)	2 (0.6)
Respiratory, thoracic and mediastinal disorders			
Cough	8 (1.6)	7 (2.1)	6 (1.8)
Psychiatric Disorders			
Depression	3 (0.6)	7 (2.1)	2 (0.6)

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

1 Upper respiratory tract infection includes the following reported preferred terms (PTs): nasopharyngitis, influenza, upper respiratory tract infection, pharyngitis, rhinitis, sinusitis, pharyngitis bacterial, tonsillitis, acute tonsillitis, laryngitis, viral pharyngitis, and viral upper respiratory tract infection.

2 Urinary tract infection includes the following reported PTs: urinary tract infection, Escherichia urinary tract infection, prostatitis, and pyelonephritis.

3 Genital infection includes the following reported PTs: vulvovaginal mycotic infection, balanoposthitis, genital infection fungal, vaginal infection, and vulvovaginitis.

4 Dyslipidaemia includes the following reported PTs: dyslipidaemia, hyperlipidaemia, hypertriglyceridaemia and hypercholesterolaemia.

Additional adverse reactions occurring at frequency of ≥2% and more than ≥1% more frequently compared to placebo in the mono-component clinical programs for saxagliptin and dapagliflozin included gastroenteritis, vomiting and polyuria.

Additional clinical trials for up to 52 weeks in adult subjects compared the combination therapy of saxagliptin 5 mg and dapagliflozin 10 mg plus metformin to active/placebo comparators of basal

insulin, sitagliptin, 1-6 mg glimepiride (a sulfonylurea), with all comparator arms on a background of ≥1,500 mg metformin. Trials did not include patients with an eGFR <60 mL/min/1.73m^2. In this patient population the safety results demonstrated that the combination of saxagliptin and dapagliflozin plus metformin is well tolerated and is consistent with the known safety profiles for the pooled safety analysis of saxagliptin 5 mg and dapagliflozin 10 mg combination plus metformin, and its monocomponents.

Diabetic ketoacidosis was identified with a frequency of rare (≥ 1/10,000 to < 1/1000), based on annual rate, in a large cardiovascular outcomes study with dapagliflozin in patients with type 2 diabetes.

Description of selected adverse events

The information below provides additional information regarding adverse events reported for the saxagliptin/dapagliflozin combination.

Hypoglycaemia

The overall incidence of hypoglycaemia for the pooled safety data patients was low (2.0%) in the saxagliptin 5 mg plus dapagliflozin 10 mg plus metformin group, 0.6% in the saxagliptin plus metformin group, and 2.3% in dapagliflozin plus metformin group.

Saxagliptin and dapagliflozin plus metformin had lower incidence rates of hypoglycaemia compared to insulin or sulfonylurea The overall incidence rates of hypoglycaemia for a 24-week study were 12.7% for the combination therapy plus metformin versus 33.1% for insulin plus metformin without sulfonylurea. The overall incidence rates for hypoglycaemia for two 52-week studies comparing the combination therapy plus metformin to glimepiride were: 4.2% for the 1st study for the combination therapy plus metformin versus 27.9% for glimepiride plus metformin and 2.9% for dapagliflozin plus metformin; for the 2nd study 18.5% for the combination therapy plus metformin versus 43.1% for glimepiride plus metformin.

No episodes of major hypoglycaemia were reported in trials with the combination therapy plus metformin and no subject discontinued the study treatment due to hypoglycaemia.

Urinary Tract Infections

In the pooled safety analysis, urinary tract infections were balanced across the 3 treatment groups: 5.7% in the saxagliptin and dapagliflozin plus metformin group, 7.4% in the saxagliptin plus metformin group and 5.6% in the dapagliflozin plus metformin group. The majority of the urinary tract infection adverse events were reported in females (81% of subjects with urinary tract infection), and were mild or moderate in intensity, of single occurrence, and most patients continued on therapy.

Genital Infections

The reported adverse events of vulvovaginitis, balanitis and related genital infections from pooled safety analysis were reflective of the safety profile with dapagliflozin. Adverse events of genital infection were reported in 3.0% in the saxagliptin and dapagliflozin plus metformin group, 0.9% of saxagliptin plus metformin group and 5.9% of subjects in the dapagliflozin plus metformin group. The majority of the genital infections were reported in females (84% of subjects with a genital infection), and were mild or moderate in intensity, of single occurrence and most patients continued on therapy.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Dapagliflozin

In the dapagliflozin cardiovascular outcomes study with 17,160 patients with type 2 diabetes mellitus and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported on treatment, one in the dapagliflozin-treated group and 5 in the placebo group.

Diabetic ketoacidosis (DKA)

Dapagliflozin

In a large cardiovascular outcomes study with dapagliflozin in patients with type 2 diabetes, where 8574 patients received dapagliflozin 10 mg and 8569 patients received placebo, with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population (see Section 4.4 Special Warnings and Precautions for Use).

Volume depletion

Events related to volume depletion (hypotension, dehydration, and hypovolemia) were reflective of the adverse events with dapagliflozin and were reported in two subjects (0.4%) in the saxagliptin and dapagliflozin plus metformin group (SAE of syncope and an adverse event of urine output decreased), and 3 subjects (0.9%) in the dapagliflozin plus metformin group (2 adverse events of syncope and 1 of hypotension).

Events Related to Decreased Renal Function

Use of dapagliflozin was associated with increases in serum creatinine and decreases in eGFR. These changes were observed to reverse after treatment discontinuation, suggesting acute haemodynamic changes play a role in the renal function abnormalities observed with dapagliflozin.

Renal-related adverse reactions (e.g. acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with dapagliflozin.

Saxagliptin/dapagliflozin combination

In the pooled safety analysis, the incidence of adverse events related to decreased renal function was 2.0% of subjects in the saxagliptin and dapagliflozin plus metformin group, 1.8% of subjects in the saxagliptin plus metformin group, and 0.6% of subjects in the dapagliflozin plus metformin group. Subjects with adverse events of renal impairment had lower mean eGFR values at baseline of 61.8 mL/min/1.73m^2 compared to 93.6 mL/min/1.73m^2 in overall population. The majority of events were considered non-serious, mild or moderate in intensity, and resolved.

Cardiovascular Safety

In the pool of three studies, CV events that were adjudicated and confirmed as CV events were reported in a total of 1.0% of subjects in the saxagliptin plus dapagliflozin plus metformin group, 0.6% in the saxagliptin plus metformin group, and 0.9% in the dapagliflozin plus metformin group.

No cardiovascular outcomes studies have been conducted to evaluate the saxagliptin/dapagliflozin combination.

In the Saxagliptin Assessment of Vascular Outcomes Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, an increase in the rate of hospitalisation for heart failure was observed in the saxagliptin-treated patients compared to placebo, although a causal relationship has not been established.

In the Dapagliflozin Effect on Cardiovascular Events (DECLARE) study, a reduced risk of hospitalisation for heart failure was observed in the dapagliflozin treated patients compared to placebo.

The overall effect of QTERN on hospitalisation for heart failure in adults with type 2 diabetes mellitus is unknown.

Vital signs

Mean change from baseline in the heart rates across the 3 treatment groups were similar. Consistent with its mild diuretic effects, the dapagliflozin-containing treatments were associated with decreases in systolic and diastolic blood pressure. The small effects on blood pressure were consistent over time. A similar proportion of subjects in each of the three treatment groups achieved systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg.

Peripheral Oedema

Saxagliptin

In a saxagliptin add-on to TZD study, the incidence of peripheral oedema was higher for saxagliptin 5 mg plus TZD versus placebo plus TZD (8.1% versus 4.3%). However, in saxagliptin monotherapy the overall incidence of peripheral oedema was similar to placebo. In the SAVOR study, the overall incidence of adverse reactions of peripheral oedema observed in patients treated with saxagliptin was similar to those treated with placebo (3.9% versus 4% respectively)

Hypersensitivity reactions

Saxagliptin

A grouping of hypersensitivity-related events in the saxagliptin 5-study pooled analysis up to Week 24 showed an incidence of 1.5% and 0.4% in patients who received saxagliptin 5 mg and placebo, respectively. None of these events in patients who received saxagliptin required hospitalisation or were reported to be life-threatening by the investigators.

Laboratory Findings

The frequency of marked abnormalities in laboratory tests results in the pooled safety analysis was low and similar across the treatment groups. (See Section 4.4 Special Warnings and Precautions for Use -Effect on laboratory tests).

Post-marketing experience

The following post-marketing case reports have been reported during post-approval use of the monocomponents. Because these cases are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency (See Section 4.4 Special Warnings and Precautions for Use).

Dapagliflozin

Metabolism and nutrition disorders – Ketoacidosis

Infections and infestations – Serious urinary tract infections such as pyelonephritis, urosepsis, necrotising fasciitis of the perineum (Fournier's gangrene)

Skin and subcutaneous tissue disorders - Rash, angioedema

Saxagliptin

Gastrointestinal disorders – acute pancreatitis

Musculoskeletal and connective tissue disorders – Arthralgia

Immune system disorders – Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.

Skin and subcutaneous tissue disorders – bullous pemphigoid

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Saxagliptin/dapagliflozin combination:

There is no information available on overdose with QTERN.

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 haemodialysis (23% of dose over four hours).

The removal of dapagliflozin by haemodialysis has not been studied.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

QTERN combines saxagliptin and dapagliflozin with distinct and complementary mechanisms of action to improve glycaemic control. Saxagliptin, through the selective inhibition of dipeptidyl peptidase-4 (DPP-4), enhances glucose-mediated insulin secretion (incretin effect). Dapagliflozin, a selective inhibitor of sodium-glucose co-transporter 2 (SGLT2), inhibits renal glucose reabsorption independently of insulin. Actions of both drugs are regulated by the plasma glucose level. The combination of both agents delivers clinically meaningful reductions in HbA1c for improved glycaemic control in patients with T2DM. While saxagliptin has a neutral effect on weight, urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric and weight loss.

Saxagliptin

Saxagliptin is a member of a class of oral anti-hyperglycaemic agents called DPP-4 inhibitors. Saxagliptin is a reversible, competitive, DPP-4 inhibitor with nanomolar potency. Saxagliptin demonstrates selectivity for DPP-4 versus other DPP enzymes, with greater than 75 fold selectivity over DPP-8 and DPP-9. Saxagliptin has extended binding to the DPP-4 active site, prolonging its inhibition of DPP-4. Saxagliptin exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Concentrations of these active intact incretin hormones are increased by saxagliptin, thereby increasing and prolonging the actions of these hormones.

Dapagliflozin

Dapagliflozin is a reversible competitive inhibitor of sodium glucose co-transporter 2 (SGLT2) with nanomolar potency that improves glycaemic control in patients with type 2 diabetes mellitus and provides cardio renal benefits.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure. Secondary effects of SGLT2 inhibition with dapagliflozin also include a modest reduction in blood pressure, reduction in body weight, and an increase in haematocrit.

The cardio-renal benefits of dapagliflozin are not solely dependent on the blood glucose lowering effect and not limited to patients with diabetes. In addition to the osmotic diuretic and related hemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis, adipokines and uric acid may be mechanisms underlying the cardio-renal beneficial effects of dapagliflozin. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24 hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal glucose, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.

The majority of the weight reduction was body fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging.

SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is approximately 1000-3000 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

Pharmacodynamic effects

Saxagliptin

In patients with type 2 diabetes, administration of saxagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent beta-cell responsiveness, which resulted in higher insulin and C peptide concentrations. The rise in insulin and the 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 dose of dapagliflozin.

Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10mg/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.

Clinical trials

Glycaemic control

Concomitant Therapy with Saxagliptin and Dapagliflozin in Patients Inadequately Controlled on Metformin

In a 24-week randomised, double-blind, superiority study comparing the combination of saxagliptin and dapagliflozin added concomitantly to metformin, versus saxagliptin or dapagliflozin added to metformin in patients with type 2 diabetes mellitus with inadequate glycaemic control on metformin alone (HbA1c ≥8% and ≤12%), the saxagliptin and dapagliflozin group achieved significantly greater reductions in HbA1c versus either the saxagliptin group or dapagliflozin group at 24 weeks (see Table 2 and Figure 1).

Table 2 HbA1c at Week 24 in Active-Controlled Study Comparing the Combination of Saxagliptin and Dapagliflozin Added Concurrently to Metformin with either Saxagliptin or Dapagliflozin Added to Metformin

Efficacy Parameter	**Saxagliptin 5 mg + Dapagliflozin 10 mg + Metformin N=179[b]**	**Saxagliptin 5 mg + Metformin N=176[b]**	**Dapagliflozin 10 mg + Metformin N=179[b]**
HbA1c (%) at week 24[a]			
Baseline (mean)	8.93	9.03	8.87
Change from baseline (adjusted mean) (95% CI)	−1.47 (−1.62, −1.31)	−0.88 (−1.03, −0.72)	−1.20 (−1.35, −1.04)
Difference from saxagliptin+metformin (adjusted mean[c]) (95% CI)		−0.59[d] (−0.81, −0.37)-	-
Difference from dapagliflozin+metformin (adjusted mean[c]) (95% CI)		-	−0.27[e] (−0.48, −0.05)-

[a] LRM = Longitudinal repeated measures (using values prior to rescue).

[b] Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.

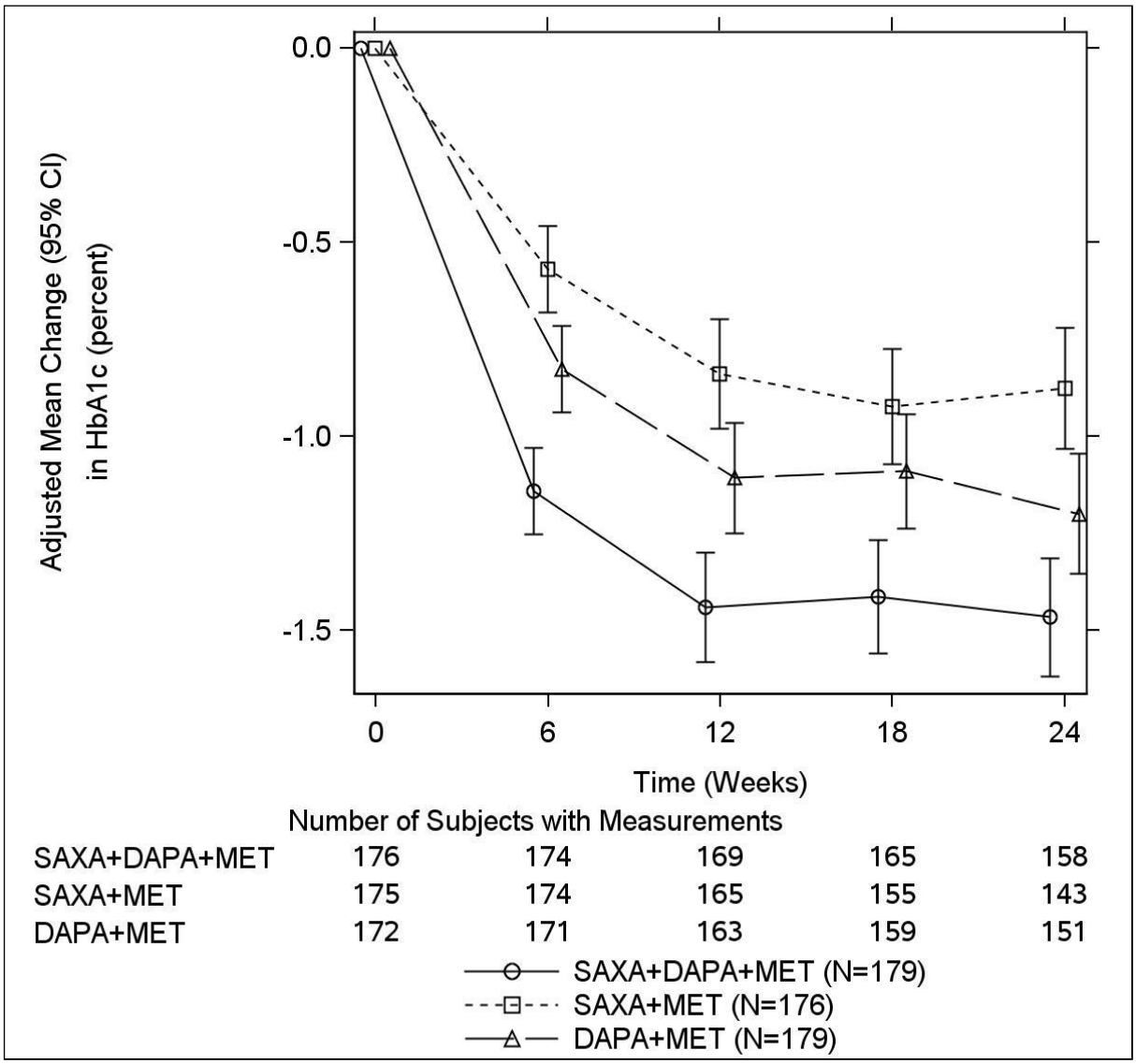
[c] Least squares mean adjusted for baseline value.

[d] p-value < 0.0001.

[e] p-value=0.0166

CI-Confidence Interval

Figure 1 **Change from Baseline in HbA1c – 24-Week Double Blind Period in Randomised Subjects***



*N is the number of randomised subjects with at least one dose of double-blind medication during short-term double-blind treatment. Mean refers to mean change from baseline based on a mixed model with treatment, baseline value, week, week-by-treatment interaction, and week-by-baseline interaction as independent variables. Error bars represent 95% confidence intervals for the adjusted mean change from baseline. Plot uses data values from healthy subjects prior to rescue. CI=Confidence Interval; saxa=saxagliptin; dapa=dapagliflozin; met=metformin

The majority of patients in this study had a baseline HbA1c of >8% (Table 3). The combination of saxagliptin and dapagliflozin added to metformin treatment consistently demonstrated greater reductions in HbA1c irrespective of baseline HbA1c, compared with saxagliptin or dapagliflozin alone added to metformin. In a separate pre-specified subgroup analysis, mean reductions from baseline in HbA1c were generally greater for patients with higher baseline HbA1c values.

Table 3 HbA1c Subgroup Analysis by Baseline HbA1c at Week 24 in Randomised Subjects

Treatments	Adjusted mean change from baseline by baseline HbA1c		
	<8.0%	**≥8% to<9%**	**≥9.0%**
Saxagliptin+Dapagliflozin +Metformin Adjusted mean change from baseline (95% CI)	–0.80 (n=37) (–1.12, –0.47)	–1.17 (n=56) (–1.44, –0.90)	–2.03 (n=65) (–2.27, –1.80)
Saxagliptin+Metformin Adjusted mean change from baseline (95% CI)	–0.69 (n=29) (–1.06, –0.33)	–0.51 (n=51) (–0.78, –0.25)	–1.32 (n=63) (–1.56, –1.09)
Dapagliflozin+Metformin Adjusted mean change from baseline (95% CI)	–0.45 (n=37) (–0.77, –0.13)	–0.84 (n=52) (–1.11, –0.57)	–1.87 (n=62) (–2.11, –1.63)

n = number of subjects with non-missing baseline and a Week 24 value.

CI= Confidence Interval

Proportion of patients achieving HbA1c <7%

Forty-one point four percent (41.4%) (95% CI [34.5, 48.2]) of patients in the saxagliptin and dapagliflozin combination group achieved HbA1c levels of less than 7% compared to 18.3% (95% CI [13.0, 23.5]) patients in the saxagliptin group and 22.2% (95% CI [16.1, 28.3]) patients in the dapagliflozin group.

Concomitant therapy of saxagliptin 5 mg and dapagliflozin 10 mg in comparison to glimepiride in patients inadequately controlled on metformin

A 52-week randomised, double-blind, active-controlled, parallel-group study with a blinded 104-week extension compared orally once daily saxagliptin 5 mg and dapagliflozin 10 mg co-administered in combination with metformin to once daily glimepiride (a sulphonylurea) up-titrated 1-6 mg plus placebo with metformin (≥1500 mg per day) in T2DM patients with inadequate glycaemic control (HbA1c ≥7.5% and ≤10.5%) on metformin alone. Patients on glimepiride/placebo dose were up-titrated starting at 1 mg per day over 12 weeks to optimal glycaemic effect (FPG <6.1 mmol/L) or the highest tolerable dose during the first 12 weeks. Thereafter, glimepiride/placebo dose were kept constant, except for down-titration to prevent hypoglycaemia.

Saxagliptin 5 mg and dapagliflozin 10 mg plus metformin had a statistically greater mean reduction in HbA1c from baseline at Week 52, compared with glimepiride plus metformin, demonstrating superiority (Table 4).

Fewer treatment intensification events occurred in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group (n=3) compared with the glimepiride plus metformin group (n=19). A total of 3 subjects (1.3%) in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group and 18 subjects (8.3%) in the glimepiride plus metformin group were rescued during the treatment period. The most common rescue treatment was insulin (2 subjects [0.9%] in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group and 11 subjects [5.1%] in the glimepiride plus metformin group).

Table 4 Results at Week 52 comparing saxagliptin 5 mg and dapagliflozin 10 mg plus metformin to glimepiride plus metformin.

Efficacy parameter*	**Saxagliptin 5 mg and Dapagliflozin 10 mg + Metformin N[a]=218**	**Glimepiride 1 to 6 mg + Metformin N[a]=212**
HbA1c (%)		
Baseline (mean)	8.4	8.49
Change from baseline (adjusted mean[b])	-1.35	-0.98
Difference from glimepiride +metformin (95% CI)	−0.37 (−0.57, −0.18) p-value <0.001	

*Mixed model of repeated measure analysis prior to rescue and treatment discontinuation.

[a]Number of subjects in the randomised subject data set with non-missing baseline assessment and at least one post-baseline assessment. Subjects had a high mean baseline HbA1c of 8.45% and a mean duration of T2DM of7.8 years across all treatment groups while on a stable metformin dose of at least 1500 mg/day (characteristics of difficult-to-treat patients).

[b]Median exposure to study medication was 365 days for all treatment groups

Proportion of patients achieving HbA1c <7%

The proportion of patients achieving HbA1c <7.0% at Week 52 was higher in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group (44.3% 95% CI [37.45, 51.32]) compared to the glimepiride plus metformin group (34.3% 95% CI [27.87, 41.33] p = 0.044).

Systolic blood pressure

The decrease in systolic blood pressure at Week 52 in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group (-2.6 mmHg 95% CI [-4.4, -0.8]) was greater than in the glimepiride plus metformin group (1.0 mmHg 95% CI [-0.9, 2.9]). The difference in mean systolic blood pressure between treatment groups was-3.6 mmHg (95% CI [-6.3, -1.0] p = 0.007).

Body weight

Treatment with saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group resulted in significant difference in mean body weight change at Week 52 compared to glimepiride plus metformin. The adjusted mean change from baseline was -3.11 kg (95% CI [-3.65, -2.57]) for the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group, and 0.95 kg (95% CI [0.38, 1.51]) for the glimepiride plus metformin group. The difference in mean body weight between treatment groups was -4.06 kg (95% CI [-4.84, -3.28] p <0.001).

Concomitant therapy of saxagliptin 5 mg and dapagliflozin 10 mg in comparison to insulin glargine in patients inadequately controlled on metformin with or without a sulfonylurea

A 24-week randomised, open-label, active-controlled, parallel-group study with a 28-week extension compared orally once daily saxagliptin 5 mg and dapagliflozin 10 mg co-administered with metformin with or without a sulfonylurea to titrated subcutaneous insulin glargine co-administered with metformin with or without a sulfonylurea in T2DM patients with inadequate glycaemic control (HbA1c ≥8.0% and ≤12.0%).

Saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a sulfonylurea group met the predefined criteria for non-inferiority in HbA1c reduction from baseline compared to insulin glargine plus metformin with or without a sulfonylurea group after 24 weeks of open-label treatment.

Table 5 Results at Week 24 comparing saxagliptin 5 mg and dapagliflozin 10 mg to insulin glargine

Efficacy parameter*	**Saxagliptin 5 mg and Dapagliflozin 10 mg + Metformin with or without a Sulfonylurea** **N[ab]=319**	**Insulin glargine + Metformin with or without a Sulfonylurea** **N[ab]=312**
HbA1c (%)		
Baseline (mean)	9.04	9.04
Change from baseline (adjusted mean[b])	-1.67	-1.54
Difference from insulin glargine + metformin with or without a SU (adjusted mean [b]) (95% CI)	−0.13 (−0.30, 0.03)	

*MMRM model with terms for strata, treatment, baseline HbA1c, week, treatment-by-week interaction and baseline HbA1c-by-week interaction. Values recorded after rescue or collected more than 8 days after the last dose date were excluded from the analysis.

[a]Subjects had a high mean baseline HbA1c of 9.05% and a mean duration of T2DM of 9.41 years across treatment groups while on a stable metformin dose of at least 1500 mg/day (characteristics of difficult-to-treat patients)

[b]Median exposure to study medication was 169 days in both treatment groups.

Hypoglycaemia events with glucose ≤3.9 mmol/L

A substantially lower proportion of patients in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a sulfonylurea group (11.4% of N=324) experienced at least one event of hypoglycaemia (glucose ≤3.9 mmol/L with symptoms) at Week 24) than the titrated insulin glargine plus metformin with or without a sulfonylurea group (24.5% of N=319). There were 57 events of hypoglycaemia in 26 patients with SU and 16 events in 11 patients without sulfonylurea in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group; there were 233 events of hypoglycaemia in 52 patients with sulfonylurea and 65 events in 26 patients without sulfonylurea in the insulin glargine plus metformin group.

Continuous glucose monitoring

After 2 weeks of open-label treatment, patients in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a sulfonylurea group demonstrated a mean decrease from baseline in 24-hour mean glucose as measured by 24-hour continuous glucose monitoring (CGM) of -2.69 mmol/L (95% CI [-2.97, -2.42]) compared to the insulin glargine plus metformin with or without a sulfonylurea group -1.58 mmol/L (95% CI [-1.86, -1.31]). The difference in the least squared mean change between the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a sulfonylurea group and insulin glargine plus metformin with or without a sulfonylurea group was -1.11 mmol/L (95% CI [-1.50, -0.72]) $p < 0.0001$).

Body weight

Treatment with saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a sulfonylurea group resulted in significant difference in body weight change at Week 24, mean change from baseline -1.50 kg (95% CI [-1.89, -1.11]) versus 2.14 kg (95% CI [1.75, 2.54]) in the insulin glargine plus metformin with or without a sulfonylurea group. The difference in mean body weight between treatment groups was -3.64 kg (95% CI [-4.20, -3.09] $p < 0.001$).

Proportion of patients achieving HbA1c < 7%

The adjusted percent (95% CI) of patients achieving a therapeutic glycaemic response (HbA1c < 7%) at Week 24 was 33.2% (28.0, 38.8) in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without sulfonylurea group and 33.5% (28.3, 39.3) in the insulin glargine plus metformin with or without sulfonylurea group (difference -0.4% 95% CI [-7.42, 6.54]). Non-inferiority of saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without sulfonylurea

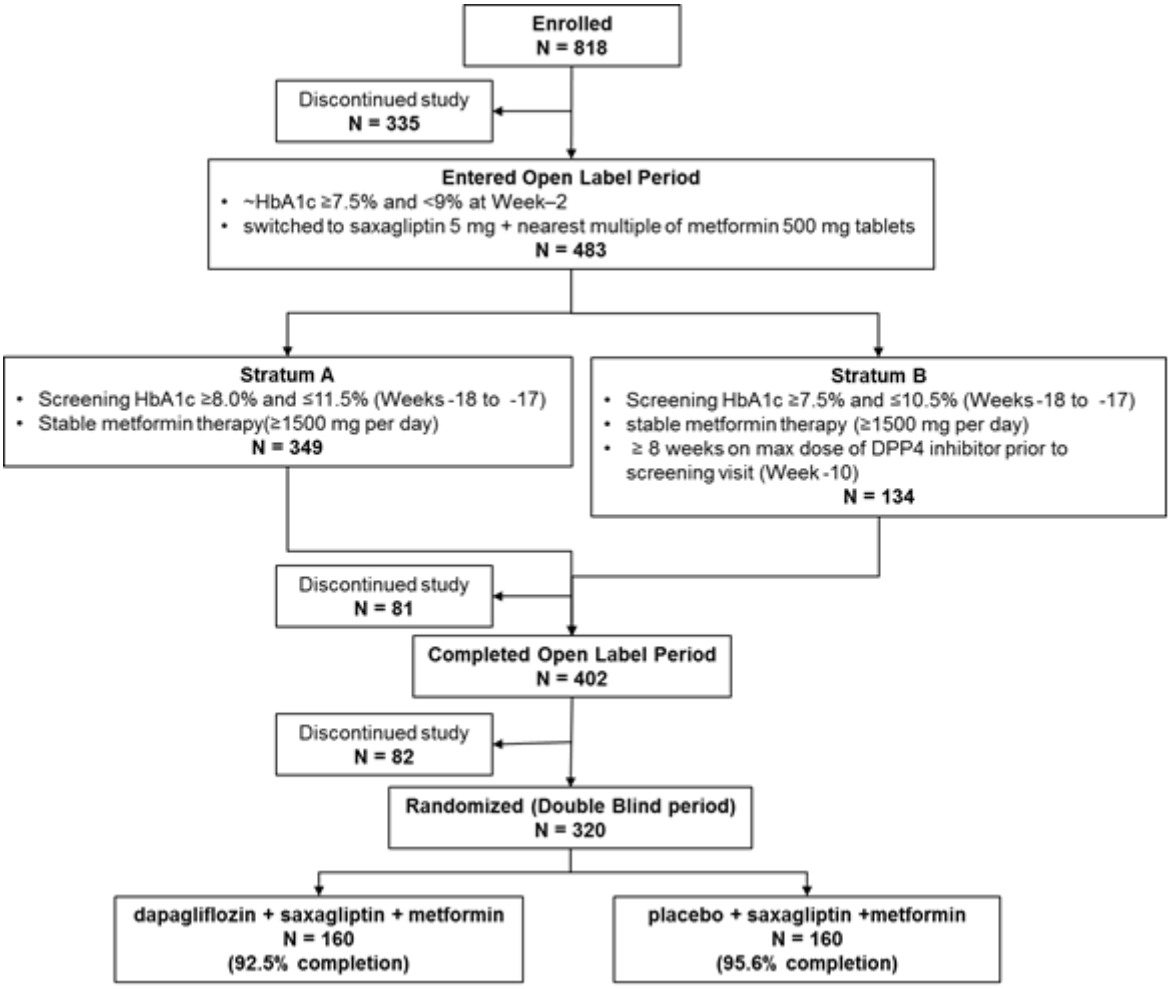
compared with the insulin glargine plus metformin with or without sulfonylurea group was demonstrated (non-inferiority defined by lower bound of 95% CI > 10%).

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

In a 24-week randomised, double-blind, placebo-controlled study with the sequential addition of 10 mg dapagliflozin to 5 mg saxagliptin and metformin was compared to the addition of placebo to 5 mg saxagliptin and metformin in patients with inadequate glycaemic control (HbA1c ≥7% and ≤10.5% at Week-2). Subject disposition for this study is presented in Figure 2.

Mean duration of diabetes was 7.6 years at randomised baseline. Patients who completed the initial 24-week study period were eligible to enter a controlled 28-week long-term study extension (52 weeks).

Figure 2 Study 2 - Subject Disposition



The safety profile of dapagliflozin added to saxagliptin plus metformin in the long-term treatment period was consistent with that previously observed in the clinical trial experience for the concomitant therapy study and that observed in the 24-week treatment period in this study.

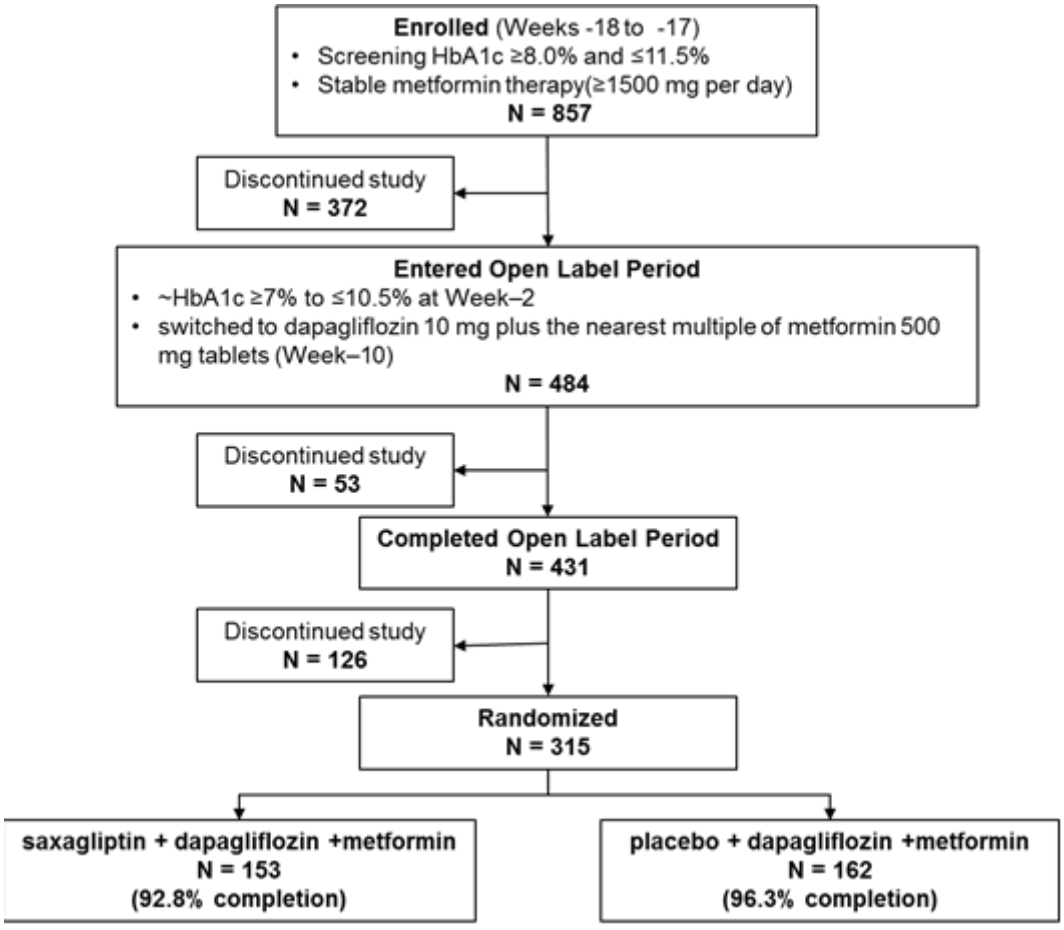
The group with dapagliflozin sequentially added to saxagliptin and metformin achieved statistically significantly (p-value <0.0001) greater reductions in HbA1c versus the group with placebo sequentially added to saxagliptin plus metformin group at 24 weeks (see Table 6). The effect in HbA1c observed at Week 24 was sustained at Week 52.

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

In a 24-week randomised, double-blind, placebo-controlled study with the sequential addition of saxagliptin 5 mg to dapagliflozin 10 mg and metformin was compared to the addition of placebo to dapagliflozin 10 mg (SGLT2 inhibitor) and metformin in subjects with T2DM with inadequate glycaemic control (HbA1c ≥7% and ≤10.5%) on metformin and dapagliflozin. Subject disposition for this study is presented in Figure 3.

Mean duration of diabetes was 7.7 years at randomised baseline. Patients who completed the initial 24-week study period were eligible to enter a controlled 28-week long-term study extension (52 weeks).

Figure 3 Study 2 Subject Disposition



The safety profile of saxagliptin added to dapagliflozin plus metformin in the long-term treatment period was consistent with that previously observed in the clinical trial experience for the concomitant therapy study and that observed in the 24-week treatment period in this study.

The group with saxagliptin sequentially added to dapagliflozin and metformin achieved statistically significant (p-value <0.0001) greater reductions in HbA1c versus the group with placebo sequentially added to dapagliflozin plus metformin group at 24 weeks (see Table 6). The effect in HbA1c observed at Week 24 was sustained at Week 52.

Table 6 HbA1c change from baseline at Week 24 and Week 52 (excluding data after rescue) for randomised subjects in studies assessing sequential addition of saxagliptin or dapagliflozin to a background of dapagliflozin and metformin or saxagliptin and metformin respectively

Efficacy parameter	Dapagliflozin added to saxagliptin + metformin therapy		Saxagliptin added to dapagliflozin + metformin therapy	
	Dapa 10 mg added to Saxa 5 mg+Met (N=160)[a]	Placebo + Saxa 5 mg+Met (N=160)[a]	Saxa 5 mg add to Dapa 10 mg+Met (N=153)[a]	Placebo + Dapa 10 mg+Met (N=162)[a]
HbA1c (%) at Week 24				
Baseline (mean)	8.24	8.16	7.95	7.85
Change from baseline (adjusted mean[b]) (95% CI)	−0.82 (−0.96, 0.69)	−0.10 (−0.24, 0.04)	−0.51 (−0.63, −0.39)	−0.16 (−0.28, −0.04)
Difference in HbA1c effect Adjusted mean[b] (95% CI) p-value	−0.72 (−0.91, −0.53) <0.0001		−0.35 (−0.52, −0.18) <0.0001	
HbA1c (%) at Week 52				
Baseline (mean)	8.24	8.16	7.95	7.85
Change from baseline (adjusted mean) (95% CI)	-0.74 (-0.90, -0.57)	0.07 (-0.90, -0.57)	-0.38 (-0.53, -0.22)	0.05 (-0.11, 0.20)
Difference in HbA1c effect Adjusted mean (95% CI) p-value	-0.81 (-1.06, -0.55)		-0.42 (-0.64, -0.20)	

[a] Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.

[b] Least squares mean adjusted for baseline value.

saxa= saxagliptin; dapa=dapagliflozin; met=metformin; CI = confidence interval

Table 7 Proportion of subjects achieving therapeutic glycaemic response (HbA1c <7%) at Week 24 and Week 52 – Excluding data after rescue - randomised subjects

Efficacy parameter	Dapagliflozin added to saxagliptin + metformin therapy		Saxagliptin added to dapagliflozin + metformin therapy	
	Dapa 10 mg added to Saxa 5 mg+Met (N=160)[a]	Placebo + Saxa 5 mg+Met (N=160)[a]	Saxa 5 mg add to Dapa 10 mg+Met (N=153)[a]	Placebo + Dapa 10 mg+Met (N=162)[a]
HbA1c <7% at Week 24*				
Baseline (mean)	8.24	8.16	7.95	7.85
Proportion of subjects (adjusted percentage) (95% CI)	38.0 % (30.9, 45.1)	12.4 % (7.0, 17.9)	35.3% (28.2, 42.4)	23.1% (16.9, 29.3)

Efficacy parameter	Dapagliflozin added to saxagliptin + metformin therapy		Saxagliptin added to dapagliflozin + metformin therapy	
	Dapa 10 mg added to Saxa 5 mg+Met (N=160)[a]	**Placebo + Saxa 5 mg+Met (N=160)[a]**	**Saxa 5 mg add to Dapa 10 mg+Met (N=153)[a]**	**Placebo + Dapa 10 mg+Met (N=162)[a]**
Difference in proportion of subjects (95% CI)	25.5 % (16.7, 45.1)		12.2% (3.4, 21.0)	
HbA1c <7% at Week 52*				
Baseline (mean)	8.24	8.16	7.95	7.85
Proportion of subjects (adjusted percentage) (95% CI)	29.4% (22.7, 36.2)	12.6% (7.4, 17.9)	29.3% (22.5, 36.1)	13.1 % (8.1, 18.2)
Difference in proportion of subjects (95% CI)	16.8% (8.4, 25.2)		16.2 % (8.1, 24.2)	

[a] Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.

saxa= saxagliptin; dapa=dapagliflozin; met=metformin; CI = confidence interval

Body weight

In the concomitant therapy study, the adjusted mean change from baseline in body weight at Week-24 (excluding data after rescue) was -2.05 kg (-2.27%) in the saxagliptin 5 mg plus dapagliflozin 10 mg plus metformin group and -2.39 kg (-2.67%) in the dapagliflozin 10 mg plus metformin group, while the saxagliptin 5 mg plus metformin group had no change (0.03%). In the saxagliptin add-on study, both treatment groups had similar small mean changes in body weight at Week-24 from baseline: -0.53 kg (-0.50%) for the saxagliptin plus dapagliflozin plus metformin group and -0.51 kg (-0.55%) for the placebo plus dapagliflozin plus metformin group. In the dapagliflozin add-on study, the adjusted changes from baseline at Week 24 in body weight were -1.91 kg (-2.23%) in the dapagliflozin plus saxagliptin plus metformin group and -0.41 kg (-0.47%) in the placebo plus saxagliptin plus metformin group.

Blood pressure

Consistent with its mild diuretic effect, the pre-specified analysis of dapagliflozin-containing treatments in the three studies were associated with decreases from baseline in systolic and diastolic blood pressure. Treatment with saxagliptin/dapagliflozin combination resulted in change from baseline for systolic blood pressure ranging from -1.3 to -2.2 mmHg and for diastolic blood pressure ranging from -0.5 to -1.2 mmHg. The modest lowering effects on BP were consistent over time and a similar number of subjects had systolic BP <130 mmHg or diastolic BP <80 mmHg at Week-24 across the treatment groups.

Supportive Studies

Moderate renal impairment CKD 3A (eGFR ≥ 45 to < 60 mL/min/1.73 m^2)

Dapagliflozin

The efficacy of dapagliflozin was assessed in a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m^2 who had inadequate glycaemic control on usual care.

Treatment with dapagliflozin resulted in reductions in HbA1c and body weight compared with placebo (Table 8).

Table 8 Results at Week 24 of a placebo-controlled study of dapagliflozin in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m^2

	Dapagliflozin[a] 10 mg	**Placebo[a]**
N[b]	**159**	**161**
HbA1c (%)		
Baseline (mean)	8.35	8.03
Change from baseline[b]	−0.37	−0.03
Difference from placebo[b]	−0.34*	
(95% CI)	(−0.53, −0.15)	
Body weight (kg)		
Baseline (mean)	92.51	88.30
Percent change from baseline[c]	−3.42	−2.02
Difference in percent change from placebo[c]	−1.43*	
(95% CI)	(−2.15, −0.69)	

[a] Metformin or metformin hydrochloride were part of the usual care in 69.4% and 64.0% of the patients for the dapagliflozin and placebo groups, respectively.

[b] Least squares mean adjusted for baseline value c Derived from least squares mean adjusted for baseline value

* $p \leq 0.001$

At Week 24, treatment with dapagliflozin demonstrated reductions in fasting plasma glucose (FPG) −1.19 mmol/L compared to −0.27 mmol/L for placebo ($p \leq 0.001$), and reductions in seated systolic blood pressure (SBP) −4.8 mmHg compared to −1.7 mmHg for placebo ($p < 0.05$).

The safety profile of dapagliflozin in the study was consistent with that in the general population of patients with type 2 diabetes. Mean eGFR decreased initially during the treatment period in the dapagliflozin group and subsequently remained stable during the 24-week treatment period (FORXIGA: -3.39 mL/min/1.73 m^2 and placebo: -0.90 mL/min/1.73 m^2). At 3 weeks after termination of FORXIGA, the mean change from baseline in eGFR in the dapagliflozin group was similar to the mean change in the placebo group (FORXIGA: 0.57 mL/min/1.73 m^2 and placebo: -0.04 mL/min/1.73 m^2).

For further information on clinical trial experience with saxagliptin and dapagliflozin, refer to the appropriate individual Product Information document.

5.2 PHARMACOKINETIC PROPERTIES

Saxagliptin/dapagliflozin combination:

Bioequivalence has been confirmed between the QTERN 5 mg/10 mg tablet and the individual saxagliptin 5 mg and dapagliflozin 10 mg tablets after single dose administration in the fasted state in healthy volunteers.

Administration of QTERN with a high-fat meal decreases dapagliflozin C_{max} by up to 47% and prolongs T_{max} by approximately 2 hours, but does 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 have been extensively characterised in healthy subjects and patients with type 2 diabetes. Saxagliptin was rapidly absorbed after oral administration, with maximum saxagliptin plasma concentrations (C_{max}) 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 $AUC_{(INF)}$ values for saxagliptin and its major metabolite were 78 ng•h/mL and 214 ng•h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The intra-subject coefficients of variation for saxagliptin C_{max} and AUC were less than 12%.

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 DPP-4 inhibition was 26.9 hours. The inhibition of plasma DPP-4 activity by saxagliptin for at least 24 hours after oral administration of saxagliptin is due to high potency, high affinity, and extended binding to the active site. 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 modelling suggest that the pharmacokinetics of saxagliptin and its major metabolite were similar in healthy subjects and in patients with type 2 diabetes.

Absorption

Saxagliptin

The amount of saxagliptin absorbed following an oral dose is at least 75%. The absolute oral bioavailability of saxagliptin is approximately 50% (90% CI of 48-53%). Food had relatively modest effects on the pharmacokinetics of saxagliptin in healthy subjects. Administration with a high-fat meal resulted in no change in saxagliptin C_{max} and a 27% increase in AUC compared with the fasted state. The time for saxagliptin to reach C_{max} (T_{max}) was increased by approximately 0.5 hours with food compared with the fasted state. These changes were not considered to be clinically meaningful.

Dapagliflozin

Dapagliflozin was rapidly and well absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increased proportional to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Food had relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects. Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50% and prolonged T_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

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 is not altered in various disease states (e.g., 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 DPP-4 inhibitor, half as potent as saxagliptin.

Dapagliflozin

Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide. Dapagliflozin 3-O-glucuronide, with a molar plasma AUC 52% higher than that of dapagliflozin itself at the clinical dose, is an inactive metabolite and does 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 faeces 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 oral administration of 50 mg [^{14}C] dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug. 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.

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

Renal impairment

Saxagliptin/dapagliflozin combination

Use of QTERN is not recommended in patients with eGFR <45 mL/min/1.73 m^{2}or end-stage renal disease. (See Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions for Use.)

Saxagliptin

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function. The 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 End Stage Renal Disease (ESRD) on haemodialysis. Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault formula:

Males: $\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times 1.2}{[\text{serum creatinine (micromol/L)}]}$

Females: 0.85 × value calculated using formula for males

The degree of renal impairment did not affect the C_{max} of saxagliptin or its major metabolite. In subjects with CrCL>50 mL/min (approximately corresponding to eGFR ≥45 mL/min/1.73 m^2 by MDRD eGFR equation, following post-hoc re-analysis), 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. Increases of this magnitude are not clinically relevant, therefore dosage adjustment in these patients is not recommended. In subjects with renal impairment with CrCL≤50 mL/min (approximately corresponding to eGFR <45 mL/min/1.73 m^2, following post-hoc re-analysis) or in subjects with ESRD on haemodialysis, 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. Use of saxagliptin in patients with ESRD requiring haemodialysis is not recommended.

Dapagliflozin

Dapagliflozin should not be used in patients with eGFR persistently <45 mL/min/1.73m^2. 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. At dapagliflozin 20 mg once-daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal glucose clearance or 24 hour 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-h 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 haemodialysis on dapagliflozin exposure is not known.

Hepatic impairment

Saxagliptin/dapagliflozin combination

See Section 4.4 Special Warnings and Precautions for Use .

Saxagliptin

There were no clinically meaningful differences in pharmacokinetics for subjects with mild, moderate, or severe hepatic impairment; therefore, no dosage adjustment for saxagliptin is recommended for patients with hepatic impairment. 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. These differences are not considered to be clinically meaningful.

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 in order to compare the pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between hepatic impairment groups or compared to healthy subjects. In patients with mild or moderate hepatic impairment mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively.

Body Mass Index

Saxagliptin

No dosage adjustment is recommended based on body mass index (BMI). BMI was not identified as a significant covariate on the apparent clearance of saxagliptin or its major metabolite in an exposure modelling analysis.

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. This difference is considered to be small, therefore, no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in patient with type 2 diabetes mellitus with high body weight (≥120 kg) is recommended.

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. This difference is considered to be small and based on these findings no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in patients with type 2 diabetes mellitus with low body weight (<50 kg) is recommended.

Elderly

Saxagliptin/dapagliflozin combination

See Section 4.4 Special Warnings and Precautions for Use .

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. Age was not identified as a significant covariate on the apparent clearance of saxagliptin and its major metabolite in an exposure modelling analysis.

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%]. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients >70 years old.

Paediatric and adolescent

Pharmacokinetics in the paediatric population have not been studied.

Gender

Saxagliptin/dapagliflozin combination

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 this difference is unlikely to be of clinical relevance. Gender was not identified as a significant covariate on the apparent clearance of saxagliptin and its major metabolite in an exposure modelling analysis.

Dapagliflozin

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

Race

Saxagliptin/dapagliflozin combination

QTERN may be used regardless of race.

Saxagliptin

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

Dapagliflozin

Race (White, Black [African descent], 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 (African descent) subjects (n=43) had 4.9% lower estimated mean dapagliflozin systemic exposures [90% CI range; 7.7% lower, 3.7% lower].

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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 positive in an *in-vitro* clastogenicity assay in the presence of metabolic activation. However, dapagliflozin was negative in the Ames mutagenicity assay and in a series of *in-vivo* clastogenicity studies evaluating micronuclei or DNA repair in rats at exposure multiples at least 2100 times the human exposure at the MRHD. The weight of evidence from these studies, along with the absence of tumour findings in the rat and mouse carcinogenicity studies, support that dapagliflozin is not genotoxic.

Carcinogenicity

No carcinogenicity studies have been conducted with saxagliptin and dapagliflozin in combination.

Saxagliptin

Two-year carcinogenicity studies were conducted in mice and rats. Saxagliptin did not induce tumours in mice treated at up to 600 mg/kg/day, producing exposure 1123-times that of humans at the recommended clinical dose. In rats, no increase in tumours was observed in males treated with saxagliptin at up to 150 mg/kg/day and females at up to 300 mg/kg/day (relative exposure at the highest doses, approximately 400 and 2465, respectively.

Dapagliflozin

Dapagliflozin did not induce tumours in two-year carcinogenicity studies in mice or rats at oral doses up to 40 mg/kg/day and 10 mg/kg/day respectively. These doses correspond to AUC exposure levels at least 78 times the human AUC at the MRHD of 10 mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, silicon dioxide, OPACODE monogramming ink S-1-10619 Blue (PI 13203), OPADRY II complete film coating system 85F17417 BUTTERSCOTCH (PI 107180) and OPADRY II complete film coating system 85F18422 White (PI 11376).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

QTERN 5/10 is available in Aluminium/ Aluminium blister packs of 7 and 28 tablets.

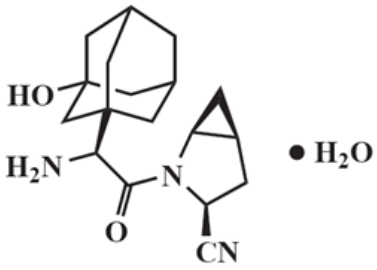
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

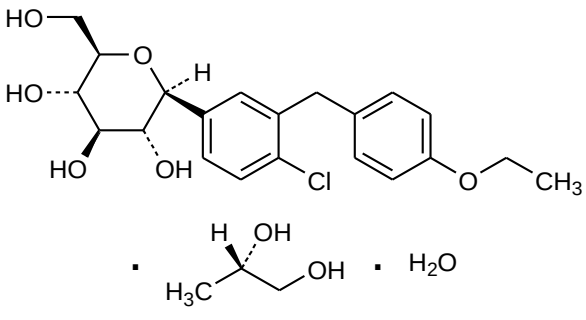
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Saxagliptin



Dapagliflozin



Chemical name	Saxagliptin is described chemically as (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxytricyclo [3.3.1.13,7] dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate	Dapagliflozin is described chemically as (1*S*)-1,5-Anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-D-glucitol, (*S*)-propylene glycol, monohydrate.
Molecular formula	$C_{18}H_{25}N_3O_2 \bullet H_2O$	$C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$
Molecular weight	333.43 (monohydrate)	502.98
Physicochemical characteristics	Saxagliptin is a white to light yellow or light brown powder, non-hygroscopic, crystalline. It is soluble in polyethylene glycol 400, acetone, acetonitrile, ethanol, isopropyl alcohol, methanol; sparingly soluble in water and slightly soluble in ethyl acetate.	Dapagliflozin drug substance is a white to off-white powder, is non-hygroscopic, crystalline. Dapagliflozin is non-ionisable; thus, its aqueous solubility and partition coefficient are not affected by changes in pH. Dapagliflozin is a Biopharmaceutical Classification System (BCS) Class III drug.

CAS number

Saxagliptin	Dapagliflozin
945667-22-1	*960404-48-2*

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

9 DATE OF FIRST APPROVAL

25 October 2016

10 DATE OF REVISION

06 September 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.5	Updated for Lithium drug-drug interaction

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Doc ID-002963835 v16.0