▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION - STEGLUJAN®
(Ertugliflozin/Sitagliptin)

1 NAME OF THE MEDICINE

Ertugliflozin / sitagliptin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

STEGLUJAN contains ertugliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor.

STEGLUJAN is available for oral use as film-coated tablets containing:

- 6.48 mg ertugliflozin pyroglutamic acid equivalent to 5 mg of ertugliflozin and 128.5 mg sitagliptin phosphate monohydrate equivalent to 100 mg of sitagliptin (STEGLUJAN 5/100)
- 19.43 mg ertugliflozin pyroglutamic acid equivalent to 15 mg of ertugliflozin and 128.5 mg sitagliptin phosphate monohydrate equivalent to 100 mg of sitagliptin (STEGLUJAN 15/100)

For the full list of excipients see Section 6.1 LIST OF EXCIPIENTS

3 PHARMACEUTICAL FORM

STEGLUJAN 5/100 are beige, almond-shaped, film-coated tablets debossed with “554” on one side and plain on the other side.

STEGLUJAN 15/100 are brown, almond-shaped, film-coated tablets debossed with “555” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

STEGLUJAN (ertugliflozin and sitagliptin phosphate monohydrate) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate

[see 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials, and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

4.2 DOSE AND METHOD OF ADMINISTRATION

General

The recommended starting dose of STEGLUJAN is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food. In patients tolerating STEGLUJAN, the dose may be increased to 15 mg ertugliflozin/100 mg sitagliptin once daily if additional glycaemic control is needed.

For patients treated with ertugliflozin who are being switched to STEGLUJAN, the dose of ertugliflozin can be maintained.

Renal impairment

Assessment of renal function is recommended prior to initiation of STEGLUJAN and periodically thereafter [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Initiation of STEGLUJAN is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2 [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

In patients with an eGFR 45 to less than 60 mL/min/1.73 m^2 tolerating STEGLUJAN containing 5 mg ertugliflozin titrate to STEGLUJAN containing 15 mg ertugliflozin as needed for glycaemic control.

Discontinue STEGLUJAN if the patient's eGFR falls persistently below 45 mL/min/1.73 m^2.

Hepatic impairment

No dose adjustment of STEGLUJAN is necessary in patients with mild or moderate hepatic impairment. STEGLUJAN has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients.

Paediatric population

Safety and effectiveness of STEGLUJAN in paediatric patients under 18 years of age have not been established.

Elderly

No dose adjustment is required based on age [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Concomitant use with insulin or an insulin secretagogue

Coadministration of STEGLUJAN with insulin or an insulin secretagogue may require lower doses of insulin or the insulin secretagogue to reduce the risk of hypoglycaemia [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

4.3 CONTRAINDICATIONS

History of a hypersensitivity reaction to STEGLUJAN, ertugliflozin, or sitagliptin phosphate or to any of the excipients.

Patients with chronic kidney disease (CKD) receiving dialysis; eGFR <30 mL/min/1.73 m^2) or eGFR persistently <45 mL/min/1.73m^2 (CKD stage 3B, 4 and 5). The efficacy of STEGLUJAN is dependent on renal function [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

STEGLUJAN should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Pancreatitis

There have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotizing pancreatitis [see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)], in patients taking sitagliptin, a component of STEGLUJAN. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin. If pancreatitis is suspected, STEGLUJAN and other potentially suspect medicinal products should be discontinued.

Hypotension/Volume depletion

Ertugliflozin, a component of STEGLUJAN, can cause intravascular volume contraction that may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine [see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients (≥65 years), or patients on diuretics may be at increased risk for volume depletion or hypotension. Before initiating STEGLUJAN in patients with one or more of these characteristics, intravascular volume status should be assessed and patients advised on the importance of adequate hydration. Monitor intravascular volume status in addition to blood pressure and renal function after initiating therapy.

In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness, heat stress or severe infections), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving STEGLUJAN. Temporary interruption of STEGLUJAN should be considered until the fluid loss is corrected.

Ketoacidosis

STEGLUJAN should not be used for the treatment of diabetic ketoacidosis.

Reports of ketoacidosis, including diabetic ketoacidosis, a serious life-threatening condition requiring urgent hospitalisation, have been identified in clinical trials and postmarketing surveillance in patients receiving sodium glucose co-transporter-2 (SGLT2) inhibitors. Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. STEGLUJAN is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with STEGLUJAN who present with signs and symptoms consistent with severe metabolic acidosis should be promptly assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with SGLT2 inhibitors may be present even if blood glucose levels are less than 14 mmol/L. If ketoacidosis is suspected, STEGLUJAN should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis generally requires insulin, fluid, potassium and carbohydrate replacement. Signs and symptoms of ketoacidosis may include excessive thirst, nausea, vomiting, abdominal pain, generalised malaise, and shortness of breath.

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

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

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

Surgery

Treatment with STEGLUJAN 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 ertugliflozin should be assessed and consideration should be given to postponing the procedure.

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

Hypoglycaemia with concomitant use with insulin and insulin secretagogues

Insulin and insulin secretagogues are known to cause hypoglycaemia. Ertugliflozin, a component of STEGLUJAN may increase the risk of hypoglycaemia when used in combination with insulin and/or an insulin secretagogue [see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Hypoglycaemia has been observed when sitagliptin, a component of STEGLUJAN, was used in combination with insulin or a sulfonylurea. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycaemia when used in combination with STEGLUJAN.

Genital mycotic infections

Ertugliflozin, a component of STEGLUJAN, increases the risk of genital mycotic infections. In trials with SGLT2 inhibitors, patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections [see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Monitor and treat appropriately.

Necrotising fasciitis of the perineum (Fournier's Gangrene)

Reports of necrotising fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotising infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including ertugliflozin. Cases have been reported in females and males. Serious outcomes have included hospitalisation, multiple surgeries, and death.

Patients treated with STEGLUJAN presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotising fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue STEGLUJAN, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycaemic control.

Caution is advised in patients at increased risk of genital infections including patients with recurrent or pre-existing urogenital infections, obesity, immunosuppressed states, smoking, alcohol abuse, end-stage renal or liver failure, and HbA1c >10%.

Hypersensitivity reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, a component of STEGLUJAN. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue STEGLUJAN, assess for other potential causes for the event, and institute alternative treatment for diabetes [See 4.3 CONTRAINDICATIONS and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Arthralgia

There have been post-marketing reports of joint pain, which may be severe, in patients taking DPP-4 inhibitors. Onset of symptoms following initiation of treatment may be rapid or may occur after longer periods. Discontinuation of therapy should be considered in patients who present with or experience an exacerbation of joint symptoms during treatment with DPP-4 inhibitors.

Bullous pemphigoid

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

Use in patients with renal impairment

STEGLUJAN
STEGLUJAN should not be used in patients with CKD stage 4 or 5 (severely impaired renal function including patients receiving dialysis; eGFR <30 mL/min/1.73 m^2) or eGFR persistently <45 mL/min/1.73m^2 (CKD stage 3B, 4 and 5) [see 4.3 CONTRAINDICATIONS].

Monitoring of renal function is recommended:

- prior to initiating STEGLUJAN and periodically thereafter, i.e. at least yearly;
- prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter;
- more frequently in patients with an eGFR below 60 mL/min/1.73 m^2.

STEGLUJAN should be discontinued when eGFR is persistently below 45 mL/min/1.73m^2 [see 4.3 CONTRAINDICATIONS].

Ertugliflozin
The efficacy of ertugliflozin is dependent on renal function.

Ertugliflozin increases serum creatinine and decreases eGFR. Patients with moderate renal impairment at baseline have larger mean changes [see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. In VERTIS CV, initiation of treatment with ertugliflozin was associated with decreases in eGFR followed by a return toward baseline. Continued treatment with ertugliflozin was associated with a slower decline in eGFR compared to placebo over time [see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

The efficacy and safety of ertugliflozin have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. Ertugliflozin is not expected to be effective in these patient populations.

Urosepsis and pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving SGLT2 inhibitors. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated [see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Discontinuation of STEGLUJAN may be considered in cases of recurrent urinary tract infections.

Use with other antidiabetic agents

The efficacy and safety of ertugliflozin in combination with GLP-1 analogues, alpha-glucosidase inhibitors and thiazolidiones has not been established.

Use in the elderly

Sitagliptin phosphate
In clinical studies, the safety and effectiveness of sitagliptin in the elderly (≥65 years) were comparable to those seen in younger patients (<65 years). No dosage adjustment is required based on age. Elderly patients are more likely to have renal insufficiency; as with other patients, dosage adjustment may be required in the presence of significant renal insufficiency

[see 4.2 DOSE AND METHOD OF ADMINISTRATION, Renal impairment]. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Ertugliflozin
Across seven Phase 3 clinical trials in the ertugliflozin development program, a total of 876 (25.7%) patients treated with ertugliflozin were 65 years and older, and 152 (4.5%) patients treated with ertugliflozin were 75 years and older. Patients 65 years and older treated with ertugliflozin had a higher incidence of adverse reactions related to volume depletion compared to younger patients; events were reported in 2.2%, 2.6%, and 1.1% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and comparator, respectively [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE REACTIONS (UNDESIRABLE EFFECTS)]. Ertugliflozin is expected to have diminished efficacy in elderly patients with renal impairment.

Paediatric use

Safety and effectiveness of STEGLUJAN in paediatric patients under 18 years of age have not been established.

Lower limb amputations

In a long-term cardiovascular outcomes study VERTIS CV, a study in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease, non-traumatic lower limb amputations (primarily of the toe) were reported with an incidence of 2.0% (0.57 subjects with event per 100 patient-years), 2.1% (0.60 subjects with event per 100 patient-years) and 1.6% (0.47 subjects with event per 100 patient-years) for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo groups respectively.
A numerical imbalance in non-traumatic lower limb amputations (primarily of the toe) was observed in patients treated with ertugliflozin across 7 Phase 3 clinical trials in the ertugliflozin development program. In these trials, 11 patients in the ertugliflozin group (0.3%) and 1 patient in the comparator group (0.1%) reported lower limb amputations. A causal association between ertugliflozin and lower limb amputation has not been definitively established.

An increase in cases of lower limb amputation (primarily of the toe) has also been observed in clinical trials with another SGLT2 inhibitor. It is important to counsel patients on routine preventative foot-care.

Effects on laboratory tests

Ertugliflozin

Positive urine glucose test
Monitoring glycaemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycaemic control.

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

STEGLUJAN

No clinically significant pharmacokinetic interaction was seen when ertugliflozin was coadministered with sitagliptin.

Pharmacokinetic drug interaction studies with STEGLUJAN have not been performed; however, such studies have been conducted with ertugliflozin and sitagliptin, the individual components of STEGLUJAN.

Drug interactions with ertugliflozin

Pharmacokinetic Interactions

Lithium
SGLT2 inhibitors, including ertugliflozin, may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after ertugliflozin initiation and dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

In vitro assessment of drug interactions
In *in vitro* studies, ertugliflozin and its two major glucuronide metabolites did not inhibit CYP450 isoenzymes (CYPs) 1A2, 2C9, 2C19, 2C8, 2B6, 2D6, or 3A4at clinically relevant concentrations, and did not induce CYPs 1A2, 2B6, or 3A4. Ertugliflozin was not a time-dependent inhibitor of CYP3A *in vitro*. As well, ertugliflozin and its two major glucuronide metabolites did not inhibit UGT1A1, 1A4, 1A6, 1A9, or 2B7 *in vitro* at clinically relevant concentrations. Only weak inhibitory activity was observed, with the IC_{50} at the most sensitive target (39 μM for ertugliflozin against UGT1A4) almost 1000 times higher than the peak plasma concentration of unbound drug in patients at the MRHD of 15 mg/day. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of drugs eliminated by these enzymes. Ertugliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters and is not a substrate of organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2), or organic anion transporting polypeptides (OATP1B1, OATP1B3, OATP2B1). Ertugliflozin or its two major glucuronide metabolites do not meaningfully inhibit P-gp, BCRP, OCT1, OCT2, OAT1, OAT3 transporters, or transporting polypeptides OATP1B1 or OATPB3 *in vitro* at clinically relevant concentrations. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are substrates of these transporters.

In vivo assessment of drug interactions
No dose adjustment of STEGLUJAN is recommended when coadministered with commonly prescribed medicinal products. Ertugliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, sitagliptin, and simvastatin in healthy subjects (see Figure 1). Coadministration of ertugliflozin with multiple doses of 600 mg once daily

rifampicin (an inducer of UGT and CYP enzymes) resulted in approximately 39% and 15% mean reductions in ertugliflozin AUC and C_{max}, respectively, relative to ertugliflozin administered alone. These changes in exposure are not considered clinically relevant. Ertugliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, sitagliptin, and simvastatin when coadministered in healthy subjects (see Figure 2).

Physiologically-based PK (PBPK) modelling suggests that coadministration of mefenamic acid (UGT inhibitor) may increase the AUC and C_{max} of ertugliflozin by 1.51- and 1.19-fold, respectively. These predicted changes in exposure are not considered clinically relevant.

Clinical studies of the effects of other drugs on the pharmacokinetics of ertugliflozin (see Figure 1)

The effects of coadministered drugs on the pharmacokinetics of ertugliflozin have been assessed in drug-drug interaction studies. There were no clinically significant drug interactions identified.

Sitagliptin
Single-dose administration of sitagliptin 100 mg had no clinically meaningful effect on the exposure of ertugliflozin 15 mg. The geometric mean ratios (GMR) and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for coadministration with sitagliptin vs. ertugliflozin alone were 102.27% (99.72%, 104.89%) and 98.18% (91.20%, 105.70%), respectively.

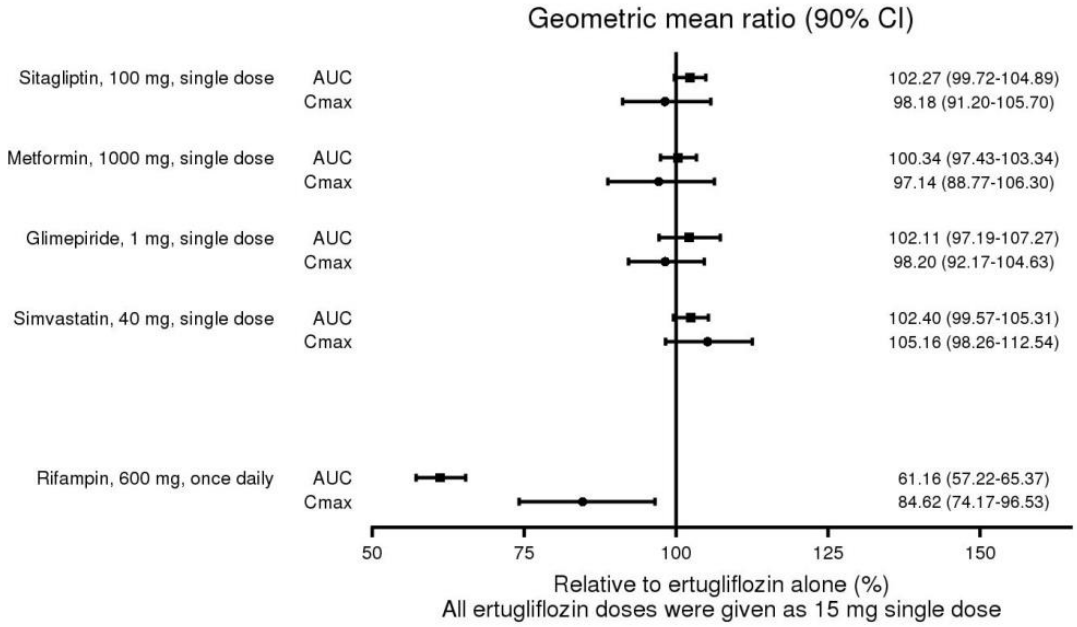
Metformin
Single-dose administration of metformin 1000 mg had no clinically meaningful effect on the exposure of ertugliflozin 15 mg. The GMR and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for coadministration with metformin vs. ertugliflozin alone were 100.34% (97.43%, 103.34%) and 97.14 % (88.77%, 106.30%), respectively.

Glimepiride
Single-dose administration of glimepiride 1 mg had no clinically meaningful effect on the exposure of ertugliflozin 15 mg. The GMR and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for coadministration with glimepiride vs. ertugliflozin alone were 102.11% (97.19%, 107.27%) and 98.20% (92.17%, 104.63%), respectively.

Simvastatin
Single-dose administration of simvastatin 40 mg had no clinically meaningful effect on the exposure of ertugliflozin 15 mg. The GMR and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for coadministration with simvastatin vs. ertugliflozin alone were 102.40% (99.57%, 105.31%) and 105.16% (98.26%, 112.54%), respectively.

Rifampicin
Multiple-dose administration of rifampicin 600 mg q.d.x 10 days was associated with a decrease in exposure of ertugliflozin 15 mg. The GMR and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for coadministration with rifampicin vs. ertugliflozin alone were 61.16% (57.22%, 65.37%) and 84.62% (74.17%, 96.53%), respectively.

Figure 1: Effects of Other Drugs on the Pharmacokinetics of Ertugliflozin



Clinical studies of the effects of ertugliflozin on the pharmacokinetics of other drugs (see Figure 2)

The effects of ertugliflozin on the pharmacokinetics of coadministered drugs have been assessed in drug-drug interaction studies. There were no clinically significant drug interactions identified.

Sitagliptin
No clinically meaningful change in sitagliptin exposure was observed following concomitant administration of a single 100 mg sitagliptin dose with 15 mg ertugliflozin compared to sitagliptin alone. The GMR and 90% CI (expressed as percentages) for sitagliptin AUC_{inf} and C_{max} for coadministration with ertugliflozin vs. sitagliptin alone were 101.67% (98.40%, 105.04%) and 101.68% (91.65%, 112.80%), respectively.

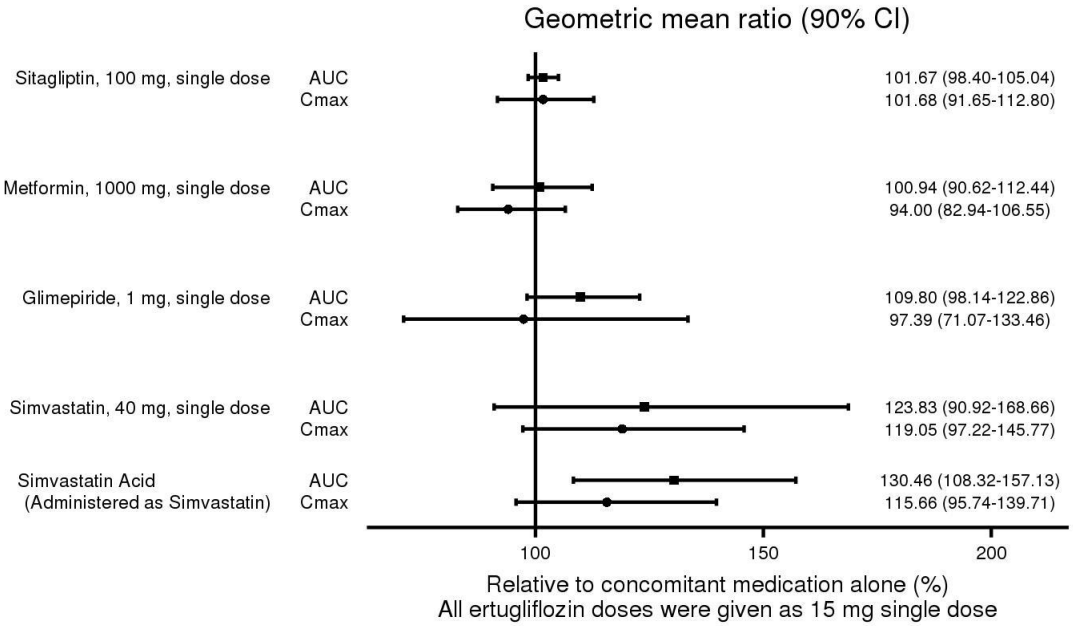
Metformin
No clinically meaningful change in metformin exposure was observed following concomitant administration of a single 1000 mg metformin dose with 15 mg ertugliflozin compared to metformin alone. The GMR and 90% CI (expressed as percentages) for metformin AUC_{inf} and C_{max} for coadministration with ertugliflozin vs. metformin alone were 100.94% (90.62%, 112.44%) and 94.00% (82.94%, 106.55%), respectively.

Glimepiride
No clinically meaningful change in glimepiride exposure was observed following concomitant administration of a single 1 mg glimepiride dose with 15 mg ertugliflozin compared to glimepiride alone. The GMR and 90% CI (expressed as percentages) for glimepiride AUC_{inf} and C_{max} for coadministration with ertugliflozin vs. glimepiride alone were 109.80% (98.14%, 122.86%) and 97.39% (71.07%, 133.46%), respectively.

Simvastatin
Coadministration of a single 40 mg simvastatin dose with a single dose of ertugliflozin 15 mg resulted in a small, non-clinically meaningful increase in AUC_{inf} and C_{max} of simvastatin and

simvastatin acid. The GMR and 90% CI (expressed as percentages) for simvastatin AUC_{inf} and C_{max} for coadministration with ertugliflozin vs. simvastatin alone were 123.83% (90.92%, 168.66%) and 119.05% (97.22%, 145.77%), respectively. The GMR and 90% CI for simvastatin acid AUC_{inf} and C_{max} for coadministration with ertugliflozin vs. simvastatin alone were 130.46% (108.32%, 157.13%) and 115.66% (95.74%, 139.71%), respectively.

Figure 2: Effects of Ertugliflozin on the Pharmacokinetics of Other Drugs



Drug interactions with sitagliptin

In Vitro assessment of drug interactions

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilise these pathways.

Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

In Vivo assessment of drug interactions

Effect of Other Drugs on Sitagliptin

Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by coadministered medications:

Metformin: Coadministration of multiple twice-daily doses of metformin with sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

Ciclosporin: A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Coadministration of a single 100-mg

oral dose of sitagliptin and a single 600-mg oral dose of ciclosporin increased the AUC and C_{max} of sitagliptin by approximately 29% and 68%, respectively. These modest changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Population Pharmacokinetics: Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on sitagliptin pharmacokinetics. Medications assessed were those that are commonly administered to patients with type 2 diabetes including cholesterol-lowering agents (e.g., statins, fibrates, ezetimibe), anti-platelet agents (e.g., clopidogrel), antihypertensives (e.g., ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (e.g., naproxen, diclofenac, celecoxib), anti-depressants (e.g., bupropion, fluoxetine, sertraline), antihistamines (e.g., cetirizine), proton-pump inhibitors (e.g., omeprazole, lansoprazole), and medications for erectile dysfunction (e.g., sildenafil).

Effect of Sitagliptin on Other Drugs
In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Multiple doses of sitagliptin slightly increased digoxin concentrations; however, these increases are not considered likely to be clinically meaningful and are not attributed to a specific mechanism.

Metformin: Co-administration of multiple twice-daily doses of sitagliptin with metformin, an OCT substrate, did not meaningfully alter the pharmacokinetics of metformin in patients with type 2 diabetes. Therefore, sitagliptin is not an inhibitor of OCT-mediated transport.

Sulfonylureas: Single-dose pharmacokinetics of glyburide, a CYP2C9 substrate, were not meaningfully altered in subjects receiving multiple doses of sitagliptin. Clinically meaningful interactions would not be expected with other sulfonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glyburide, are primarily eliminated by CYP2C9.

Simvastatin: Single-dose pharmacokinetics of simvastatin, a CYP3A4 substrate, were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP3A4-mediated metabolism.

Thiazolidinediones: Single-dose pharmacokinetics of rosiglitazone were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP2C8-mediated metabolism. Clinically meaningful interactions with pioglitazone are not expected because pioglitazone predominantly undergoes CYP2C8- or CYP3A4-mediated metabolism.

Warfarin: Multiple daily doses of sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Since S(-) warfarin is primarily metabolized by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.

Oral Contraceptives: Coadministration with sitagliptin did not meaningfully alter the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma C_{max} by 18%. These increases are not considered to be clinically meaningful.

Use with other antidiabetic agents: The safety and efficacy of sitagliptin in combination with GLP-1 mimetics, or alpha-glucosidase inhibitors has not been established.

Other Drugs: Sitagliptin has not been studied in combination with orlistat.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of STEGLUJAN or its individual components on fertility in humans has not been studied. No animal fertility studies have been performed with ertugliflozin and sitagliptin in combination.

Ertugliflozin
In rats, no effects on male or female fertility were observed with oral administration of ertugliflozin up to the highest dose of 250 mg/kg/day (yielding approximately 280 and 380 times the clinical plasma AUC for unbound ertugliflozin at the maximum recommended human dose (MRHD) of 15 mg/day in the respective sexes).

Sitagliptin
No adverse effects on fertility were observed in male and female rats given sitagliptin orally at doses up to 1000 mg/kg daily (up to approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day) prior to and throughout mating.

Use in pregnancy (Category D)

There are no adequate and well-controlled studies of STEGLUJAN or its individual components in pregnant women. Based on results from animal studies, ertugliflozin may affect renal development and maturation. No animal embryofetal development studies have been performed with ertugliflozin and sitagliptin in combination. STEGLUJAN is not recommended during pregnancy.

Ertugliflozin
In animal studies, ertugliflozin did not adversely affect developmental outcomes in rats and rabbits at oral doses up to 100 mg/kg/day and 250 mg/kg/day in the respective species (yielding approximately 240 and >1000 times the clinical AUC for unbound ertugliflozin at the MRHD of 15 mg/day). At a maternally toxic dose in rats (250 mg/kg/day), lower fetal viability and a higher incidence of cardiac malformation were observed at 510 times the clinical exposure at the MRHD, based on AUC). Ertugliflozin and/or its metabolites were shown to cross the placenta in rats. The developing kidney is seen to be more sensitive to ertugliflozin than the mature organ. When ertugliflozin was administered to juvenile rats from post-natal day (PND) 21 to PND 90, increased kidney weights, dilatation of the renal pelvis and tubules, and renal

mineralization were seen at all dose levels tested (≥5 mg/kg/day, yielding 13 times the clinical exposure at the MRHD), with effects more prominent than observed in adult animals.

Sitagliptin
Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg or in rabbits given up to 125 mg/kg during organogenesis (up to 32 and 22 times, respectively, the human exposure based on the recommended daily adult human dose of 100 mg/day). In rats, a slight increase in the incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) was observed at oral doses of 1000 mg/kg/day (approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Slight decreases in mean preweaning body weights of both sexes and postweaning body weight gains of males were observed in the offspring of rats given oral dose of 1000 mg/kg/day. Sitagliptin crosses the placenta in rats and rabbits.

Use in lactation

There is no information regarding the presence of ertugliflozin or sitagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin and sitagliptin shown to be excreted in the milk of lactating rats, with levels in milk particularly high for sitagliptin (milk:plasma ratio of 4:1). Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney, based on data with ertugliflozin [see Use in pregnancy].

Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants STEGLUJAN should not be used during breast-feeding.

4.7 EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES

STEGLUJAN has no or negligible influence on the ability to drive or use machines. However when driving or using machines, it should be taken into account that dizziness and somnolence have been reported with sitagliptin. In addition, patients should be alerted to the risk of hypoglycaemia when STEGLUJAN is used in combination with insulin or an insulin secretagogue and to the elevated risk of adverse reactions related to volume depletion, such as postural dizziness [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

Ertugliflozin and Sitagliptin
The safety of concomitantly administered ertugliflozin and sitagliptin has been evaluated in 990 patients with type 2 diabetes mellitus treated for 26 weeks in three studies; a factorial study of ertugliflozin 5 mg or 15 mg in combination with sitagliptin 100 mg once daily compared to the individual components, a placebo-controlled study of ertugliflozin 5 mg or 15 mg as add-on therapy to sitagliptin 100 mg and metformin once daily, and a placebo-controlled study of initial therapy with ertugliflozin 5 mg or 15 mg once daily in combination with sitagliptin 100 mg once daily [see 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials]. The incidence and type of adverse reactions in these three studies were similar to the adverse reactions seen with ertugliflozin and described below in Table 1. There were no additional

adverse reactions identified in these three trials that included sitagliptin relative to the three placebo-controlled studies with ertugliflozin (see below).

Ertugliflozin

Pool of placebo-controlled trials evaluating ertugliflozin 5 and 15 mg
The primary assessment of safety and tolerability was conducted in a pooled analysis of three 26-week placebo-controlled trials with similar study design, duration of treatment, and baseline characteristics. Ertugliflozin was used as monotherapy in one trial and as add-on therapy in two trials [see 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials]. These data reflect exposure of 1,029 patients to ertugliflozin with a mean exposure duration of approximately 25 weeks. Patients received ertugliflozin 5 mg (N = 519), ertugliflozin 15 mg (N = 510), or placebo (N = 515) once daily. The data in Table 1 are derived from this pooled analysis.

The overall incidence of subjects with 1 or more adverse events was not notably different across the ertugliflozin 5 mg (45.5%), ertugliflozin 15 mg (50.4%), and placebo (51.1%) groups. The incidence of non-fatal serious adverse events was low and similar in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group (3.3%, 2.4%, and 2.9% for the ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo groups, respectively). The incidence of adverse events resulting in discontinuation from study medication was low overall and not notably different in the ertugliflozin 5 mg and 15 mg groups (2.3% and 1.4%, respectively) relative to the placebo groups (1.7%).

The adverse drug reactions (ADRs) listed in Table 1 are presented by System Organ Class (SOC).

Table 1: Adverse Drug Reactions Reported in Patients Receiving Ertugliflozin

Body System/Organ Class **Adverse Reaction**	**Ertugliflozin 5 mg %**	**Ertugliflozin 15 mg %**	**Placebo %**
	N = 519	**N = 510**	**N = 515**
Infections and infestations			
Female genital mycotic infections*	9.1	12.2	3.0
Male genital mycotic infections†	3.7	4.2	0.4
Renal and urinary disorders			
Increased urination‡	2.7	2.4	1.0
Reproductive system and breast disorders			
Vulvovaginal pruritus	1.0	1.2	0.2
General disorders and administration site conditions			
Thirst§	1.3	1.0	0.2

* Includes: genital candidiasis, genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis. Percentages calculated with the number of female patients in each group as denominator: placebo (N = 235), ertugliflozin 5 mg (N = 252), ertugliflozin 15 mg (N = 245).

† Includes: balanitis candida, balanoposthitis, genital infection, and genital infection fungal. Percentages calculated with the number of male patients in each group as denominator: placebo (N = 280), ertugliflozin 5 mg (N = 267), ertugliflozin 15 mg (N = 265).

‡ Includes: pollakiuria, micturition urgency, polyuria, urine output increased, and nocturia.

§ Includes: thirst and polydipsia.

Description of selected adverse reactions

Volume depletion
Ertugliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion, particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2). In the pool of three placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., dehydration, dizziness postural, presyncope, syncope, hypotension, and orthostatic hypotension) were not more frequent in patients treated with ertugliflozin compared to those treated with placebo; events were reported by 0.8%, 1.0%, and 1.7% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. A higher incidence was seen in a study of patients with moderate renal impairment; events were reported by 4.4%, 1.9%, and 0% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. Ertugliflozin may also increase the risk of hypotension in other patients at risk for volume contraction [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Ketoacidosis
In VERTIS CV, ketoacidosis was identified in 19 (0.3%) ertugliflozin-treated patients and in 2 (0.1%) placebo-treated patients. Across seven other Phase 3 clinical trials in the ertugliflozin development program, ketoacidosis was identified in 3 (0.1%) ertugliflozin-treated patients and 0.0% of comparator-treated patients [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Impairment in renal function
Use of ertugliflozin was associated with increases in serum creatinine and decreases in eGFR [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Effects on Laboratory Tests]. Patients with moderate renal impairment at baseline had larger mean changes; these changes were observed to reverse after treatment discontinuation, suggesting acute haemodynamic changes play a role in the renal function abnormalities observed with ertugliflozin [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS, Use in Patients with Renal impairment].

In VERTIS CV initiation of treatment with ertugliflozin was associated with decreases in eGFR observed at Week 6 (-2.7, -3.8 and -0.4 mL/min/1.73m^2 for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo respectively) followed by a return toward baseline at Week 52 (-0.4, -1.1 and -0.2 mL/min/1.73m^2 for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo respectively). Continued treatment with ertugliflozin was associated with a slower decline in eGFR compared to placebo up to Week 260. In patients with moderate renal impairment, the mean change from baseline in eGFR was -0.4, -2.0 and 2.2 mL/min/1.73m^2 for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo respectively at Week 6 and 2.0, 1.1 and 3.2 mL/min/1.73m^2 for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo respectively at Week 52.

In VERTIS CV, the incidences of renal-related adverse reactions (e.g., acute kidney injury, renal impairment, acute prerenal failure) were 4.2%, 4.3% and 4.7% in patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo respectively in the general study population. In patients with moderate renal impairment, the incidences of renal-related adverse reactions were 9.7%, 10.0% and 10.2% in patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo respectively.

Hypoglycaemia

In all clinical trials, hypoglycaemia was defined as any event regardless of symptoms, where biochemical hypoglycaemia was documented (any glucose value below or equal to 3.9 mmol/L). Severe hypoglycaemia was defined as an event consistent with hypoglycaemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained).

The incidence of hypoglycaemia by study is shown in Table 2. The incidence of hypoglycaemia may be higher when ertugliflozin is administered with insulin and/or an insulin secretagogue [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Table 2: Incidence of Overall[*] and Severe[†] Hypoglycaemia in Placebo- or Comparator-Controlled Clinical Studies

Monotherapy (26 weeks)	**Ertugliflozin 5 mg (N = 156)**	**Ertugliflozin 15 mg (N = 152)**	**Placebo (N = 153)**		
Overall [N (%)]	4 (2.6)	4 (2.6)	1 (0.7)		
Severe [N (%)]	0 (0.0)	2 (1.3)	0 (0.0)		
Add-on Combination Therapy with Metformin (26 weeks)	**Ertugliflozin 5 mg (N = 207)**	**Ertugliflozin 15 mg (N = 205)**	**Placebo (N = 209)**		
Overall [N (%)]	15 (7.2)	16 (7.8)	9 (4.3)		
Severe [N (%)]	1 (0.5)	0 (0.0)	1 (0.5)		
Active-Controlled Study with Glimepiride as Add-on Combination Therapy with Metformin (52 weeks)	**Ertugliflozin 5 mg (N = 448)**	**Ertugliflozin 15 mg (N = 440)**	**Glimepiride (N = 437)**		
Overall [N (%)]	25 (5.6)	36 (8.2)	119 (27.2)		
Severe [N (%)]	1 (0.2)	1 (0.2)	10 (2.3)		
Factorial Study with Sitagliptin as Add-on Combination Therapy with Metformin (26 weeks)	**Ertugliflozin 5 mg (N = 250)**	**Ertugliflozin 15 mg (N = 248)**	**Sitagliptin (N = 247)**	**Ertugliflozin 5 mg + sitagliptin (N = 243)**	**Ertugliflozin 15 mg + sitagliptin (N = 244)**
Overall [N (%)]	14 (5.6)	13 (5.2)	9 (3.6)	13 (5.3)	22 (9.0)
Severe [N (%)]	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Add-on Combination Therapy with Metformin and Sitagliptin (26 weeks)	**Ertugliflozin 5 mg (N = 156)**	**Ertugliflozin 15 mg (N = 153)**	**Placebo (N = 153)**		
Overall [N (%)]	7 (4.5)	3 (2.0)	5 (3.3)		
Severe [N (%)]	1 (0.6)	0 (0.0)	1 (0.7)		

Initial Combination Therapy with Sitagliptin (26 weeks)			**Placebo (N = 97)**	**Ertugliflozin 5 mg + sitagliptin (N = 98)**	**Ertugliflozin 15 mg + sitagliptin (N = 96)**
Overall [N (%)]			1 (1.0)	6 (6.1)	3 (3.1)
Severe [N (%)]			0 (0.0)	0 (0.0)	2 (2.1)
In Combination with Insulin and/or an Insulin Secretagogue in Patients with Moderate Renal Impairment (26 weeks)	**Ertugliflozin 5 mg (N = 148)**	**Ertugliflozin 15 mg (N = 143)**	**Placebo (N = 133)**		
Overall [N (%)]	53 (35.8)	39 (27.3)	48 (36.1)		
Severe [N (%)]	5 (3.4)	3 (2.1)	3 (2.3)		
Add-on Combination with Insulin with or without Metformin (18 weeks)	**Ertugliflozin 5 mg (N = 348)**	**Ertugliflozin 15 mg (N = 370)**	**Placebo (N = 347)**		
Overall [N (%)]	137 (39.4)	144 (38.9)	130 (37.5)		
Severe [N (%)]	13 (3.7)	19 (5.1)	12 (3.5)		
Add-on Combination with a Sulfonylurea (18 weeks)	**Ertugliflozin 5 mg (N = 55)**	**Ertugliflozin 15 mg (N = 54)**	**Placebo (N = 48)**		
Overall [N (%)]	4 (7.3)	5 (9.3)	2 (4.2)		
Severe [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)		
Add-on Combination with Metformin and a Sulfonylurea (18 weeks)	**Ertugliflozin 5 mg (N = 100)**	**Ertugliflozin 15 mg (N = 113)**	**Placebo (N = 117)**		
Overall [N (%)]	20 (20.0)	30 (26.5)	17 (14.5)		
Severe [N (%)]	2 (2.0)	2 (1.8)	1 (0.9)		

* Overall hypoglycaemic events: plasma or capillary glucose of less than or equal to 3.9 mmol/L.
† Severe hypoglycaemic events: required assistance, lost consciousness, or experienced a seizure regardless of blood glucose.

Genital mycotic infections

In the pool of three placebo-controlled clinical trials, female genital mycotic infections (e.g., genital candidiasis, genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis) occurred in 9.1%, 12.2%, and 3.0% of females treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. In females, discontinuation due to genital mycotic infections occurred in 0.6% and 0% of patients treated with ertugliflozin and placebo, respectively [See 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

In the same pool, male genital mycotic infections (e.g., balanitis candida, balanoposthitis, genital infection, genital infection fungal) occurred in 3.7%, 4.2%, and 0.4% of males treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males. In males, discontinuations due to genital mycotic infections occurred in 0.2% and 0% of patients treated with ertugliflozin and placebo, respectively. In rare instances, phimosis was reported and sometimes circumcision was performed [See 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Urinary tract infections
In VERTIS CV, urinary tract infections (e.g., urinary tract infection, cystitis, dysuria) occurred in 12.2%, 12.0% and 10.2% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. The incidences of serious urinary tract infections were 0.9%, 0.4%, and 0.8% with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively.

Sitagliptin
In controlled clinical studies as both monotherapy and combination therapy with metformin or pioglitazone, the overall incidence of adverse reactions, hypoglycaemia, and discontinuation of therapy due to clinical adverse reactions with sitagliptin were similar to placebo (discontinuation rates: sitagliptin monotherapy, 24-week study, 2.1% vs placebo 1.6%, 18-week study 2% vs placebo 2.7%; sitagliptin add-on to metformin 2.4% vs placebo and metformin 3%; sitagliptin add-on to pioglitazone 5.7% vs placebo and pioglitazone 1.1%).

In combination with glimepiride, with or without metformin, the overall incidence of clinical adverse reactions with sitagliptin was higher than with placebo, in part related to a higher incidence of hypoglycaemia (see Table 3); the incidence of discontinuation due to clinical adverse reactions was similar to placebo (discontinuation rates: sitagliptin add-on to glimepiride, with or without metformin, 2.3% vs placebo and glimepiride, with or without metformin, 1.4%; sitagliptin add-on to metformin and a sulfonylurea, at 54 weeks, 1.4% vs placebo/pioglitazone, metformin and a sulfonylurea 3.8%). In combination with stable-dose insulin, with or without metformin, the overall incidence of clinical adverse reactions with sitagliptin was higher than placebo, in part related to a higher incidence of hypoglycaemia (see Table 3); the incidence of discontinuation due to clinical adverse reactions was slightly higher than placebo (discontinuation rates: sitagliptin add-on to insulin, with or without metformin, 3.4% vs placebo and insulin, with or without metformin, 1.3%).

Monotherapy and Add-On Combination Therapy
Two placebo-controlled monotherapy studies, one of 18- and one of 24-week duration, included patients treated with sitagliptin 100 mg daily, sitagliptin 200 mg daily, and placebo. Five 24-week, placebo-controlled add-on combination therapy studies, one with metformin, one with pioglitazone, one with glimepiride with or without metformin, one with metformin and a sulfonylurea (glimepiride or gliclazide) and one with stable-dose insulin with or without metformin were also conducted. In addition to a stable dose of metformin, pioglitazone, glimepiride, glimepiride and metformin, gliclazide and metformin, insulin, or insulin and metformin, patients whose diabetes was not adequately controlled were given either sitagliptin 100 mg daily or placebo. The adverse reactions, reported regardless of investigator assessment of causality in ≥ 5% of patients treated with sitagliptin 100 mg daily as monotherapy, sitagliptin in combination with pioglitazone, sitagliptin in combination with glimepiride, with or without metformin, or sitagliptin in combination with metformin and a sulfonylurea, or sitagliptin in combination with insulin, with or without metformin, and more commonly than in patients treated with placebo, are shown in Table 3.

Table 3: Placebo-Controlled Clinical Studies of sitagliptin Monotherapy* or Add-on Combination Therapy with Pioglitazone or Glimepiride +/- Metformin or Metformin + Sulfonylurea or Insulin +/- Metformin: Adverse Reactions Reported in ≥5% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality†

Body System/Adverse Reactions	**Number of Patients (%)**	
	Sitagliptin 100 mg	**Placebo**
	N = 443	N = 363
Infections and Infestations		
Nasopharyngitis	23 (5.2)	12 (3.3)
	Sitagliptin 100 mg + Pioglitazone	**Placebo + Pioglitazone**
	N = 175	N = 178
Infections and Infestations		
Upper Respiratory Tract Infection	11 (6.3)	6 (3.4)
Nervous System Disorders		
Headache	9 (5.1)	7 (3.9)
	Sitagliptin 100 mg + Glimepiride (+/- Metformin)	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Metabolism and Nutrition disorders		
Hypoglycaemia	27 (12.2)	4 (1.8)
Infections and Infestations		
Nasopharyngitis	14 (6.3)	10 (4.6)
Nervous System Disorders		
Headache	13 (5.9)	5 (2.3)
	Sitagliptin 100 mg + Metformin + Sulfonylurea	**Placebo + Metformin + Sulfonylurea**
	N = 210	N = 212
Metabolism and Nutrition Disorders		
Hypoglycaemia	31 (14.8)‡	10 (4.7)‡
	Sitagliptin 100 mg + Insulin (+/- Metformin)	**Placebo + Insulin (+/- Metformin)**
	N = 322	N = 319
Metabolism and Nutrition disorders		
Hypoglycaemia	50 (15.5)	25 (7.8)

† Intent to treat population
* Overall, the safety profile of the 200-mg daily dose was similar to that of the 100-mg daily dose.
‡ Weeks 0-24.

In the study of patients receiving sitagliptin as monotherapy compared to metformin, there were no adverse reactions reported regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients given placebo. In another 24-week study of patients receiving sitagliptin as add-on therapy while undergoing insulin intensification (with or without metformin), there were no drug-related adverse reactions reported that occurred with an incidence of ≥ 1% in patients treated with sitagliptin 100 mg and more commonly than in patients treated with placebo.

The adverse reactions, reported regardless of investigator assessment of causality in ≥ 5% of patients treated with sitagliptin 100 mg daily or patients treated with metformin as monotherapy are shown in Table 4.

Table 4: Initial Therapy with Sitagliptin or Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥ 5% of Patients Receiving Mono Therapy all patients "as treated"

Number of patients (%)		
	Sitagliptin	**Metformin**
	N = 528	**N = 522**
Diarrhoea	19 (3.6)	57 (10.9)

When sitagliptin was added to metformin and a sulfonylurea, over the 54-week study duration hypoglycaemia was reported in 38 (18.1%) patients treated with sitagliptin + metformin + sulfonylurea compared to 31 (14.6%) patients in the control group (placebo + metformin + sulfonylurea for 24 weeks followed by pioglitazone + metformin + sulfonylurea for 30 weeks). Symptomatic episodes assessed as likely to be hypoglycaemia were reported as adverse experiences regardless of whether fingerstick blood glucose determination was performed at the time of symptoms. Severe hypoglycaemia was noted in 2 (1.0%) patients treated with sitagliptin + metformin + sulfonylurea compared to one patient (0.5%) treated with placebo/pioglitazone + metformin + sulfonylurea.

Adverse reactions reported in 2% to 5% of patients treated with sitagliptin in these studies and at least 2 fold more commonly than in patients treated with placebo are listed below:

Sitagliptin monotherapy (24-week study)
Gastrointestinal Disorders: Constipation
*Infections and Infestations***:** Pharyngitis
Vascular Disorders: Hypertension

Sitagliptin monotherapy (18-week study)
Musculoskeletal and Connective Tissue Disorders: Back pain, osteoarthritis, pain in extremity

Sitagliptin with metformin
Musculoskeletal and Connective Tissue Disorders: Arthralgia

Sitagliptin with pioglitazone
Psychiatric Disorders: Depression

Sitagliptin with glimepiride (with or without metformin)
Gastrointestinal Disorders: Abdominal pain upper, constipation, dyspepsia
Infections and Infestations: Bronchitis, gastroenteritis, influenza
Musculoskeletal and Connective Tissue Disorders: Back pain, pain in extremity

Sitagliptin with metformin and a sulfonylurea (with or without metformin)
Infections and Infestations: Influenza, nasopharyngitis
Musculoskeletal and Connective Tissue Disorders: Pain in extremity

Sitagliptin with insulin (with or without metformin)
Nervous system disorders: Headache

Adverse reactions reported in 2% to 5% of patients treated with sitagliptin and at least 2 fold more commonly than in patients treated with metformin are listed below:

Sitagliptin monotherapy versus metformin (24-week study)
Vascular Disorders: Hypertension

Initial Combination Therapy
In an additional, 24-week, placebo-controlled factorial study of initial therapy with sitagliptin in combination with metformin, the adverse reactions reported (regardless of investigator assessment of causality) in ≥ 5% of patients are shown in Table 5.

Table 5: Initial Therapy with Combination of Sitagliptin and Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥ 5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)†

	Number of Patients (%)			
	Placebo/ Metformin 1000 mg bid	**Sitagliptin 100 mg QD**	**Metformin 500 or 1000 mg bid ††**	**Sitagliptin 50 mg bid + Metformin 500 or 1000 mg bid††**
	N = 176	N = 179	N = 364††	N = 372††
Diarrhoea	12 (6.8)	8 (4.5)	37 (10.1)	44 (11.8)
Nausea	4 (2.3)	2 (1.1)	25 (6.9)	22 (5.9)
Bronchitis	8 (4.5)	3 (1.7)	14 (3.8)	27 (7.3)
Influenza	5 (2.8)	8 (4.5)	25 (6.9)	20 (5.4)
Upper Respiratory Tract Infection	13 (7.4)	12 (6.7)	37 (10.2)	45 (12.1)
Urinary Tract Infection	4 (2.3)	0 (0)	21 (5.8)	19 (5.1)
Arthralgia	3 (1.7)	7 (3.9)	18 (4.9)	20 (5.4)
Back Pain	9 (5.1)	9 (5.0)	16 (4.4)	24 (6.5)
Headache	7 (4.0)	6 (3.4)	21 (5.8)	27 (7.3)

† Intent-to-treat population.
†† Data pooled for the patients given the lower and higher doses of metformin.

Adverse reactions of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The overall incidence of pre-specified adverse reactions of hypoglycaemia in patients with type 2 diabetes inadequately controlled on diet and exercise was 2.8% in patients given placebo, 1.1% in patients given sitagliptin alone, 1.9% in patients given metformin alone, and 3.8% in patients given sitagliptin in combination with metformin.

Treatment-emergent adverse events were reported in similar numbers across all treatment groups. Over the two-year treatment period, discontinuation due to loss of efficacy was reported more commonly in the 100 mg sitagliptin group than other treatment groups.

Adverse reactions reported in 2% to 5% of patients treated with sitagliptin in this study and at least 2 fold more commonly than in patients treated with placebo/active comparator are listed below:

Initial therapy with sitagliptin
Gastrointestinal disorders: Abdominal pain upper, constipation
Infections and infestations: Gastroenteritis
Musculoskeletal and connective tissue disorders: Arthralgia

Pooled Analysis
In the pre specified pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the overall incidence of adverse experiences of hypoglycaemia in patients treated with sitagliptin 100 mg was similar to placebo (1.2% vs. 0.9%). Adverse experiences of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The incidence of selected gastrointestinal adverse reactions in patients treated with sitagliptin or placebo was as follows: abdominal pain (sitagliptin, 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), vomiting (0.8%, 0.9%), and diarrhoea (3.0%, 2.3%).

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with sitagliptin.

Pancreatitis
In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomised to receive sitagliptin 100 mg/day (N = 5,429) or corresponding (active or placebo) control (N = 4,817), the incidence of non-adjudicated acute pancreatitis events was 0.1 per 100 patient-years in each group (4 patients with an event in 4,708 patient-years for sitagliptin and 4 patients with an event in 3,942 patient-years for control) [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Pancreatitis] [See also *TECOS Cardiovascular Safety Study*, below.]

TECOS Cardiovascular safety study
The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥30 and <50 mL/min/1.73 m^2), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA1c and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.7% in sitagliptin-treated patients and 2.5% in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 1.0% in sitagliptin-treated patients and 0.7% in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3% in sitagliptin-treated patients and 0.2% in placebo-treated patients.

Laboratory tests

Ertugliflozin

Increases in serum creatinine and decreases in eGFR
Initial increases in mean creatinine and decreases in mean eGFR in patients treated with ertugliflozin were generally transient during continuous treatment. In the pool of three placebo-controlled clinical trials, mean changes from baseline in creatinine at 6 weeks were 2.41 and 2.76 µmol/L for ertugliflozin 5 mg and 15 mg, respectively, compared to 0.24 µmol/L for placebo. Mean changes from baseline in eGFR were -2.7 and -3.1 mL/min/1.73 m^2 for ertugliflozin 5 mg and 15 mg, respectively, compared to -0.3 mL/min/1.73 m^2 for placebo. At 26 weeks, mean changes from baseline in creatinine were -0.08 and 0.80 µmol/L for ertugliflozin 5 mg and 15 mg, respectively, compared to -0.57 µmol/L for placebo. Mean changes from baseline in eGFR at 26 weeks were 0.5 and -0.6 mL/min/1.73 m^2 for ertugliflozin 5 mg and 15 mg, respectively, compared to 0.7 mL/min/1.73 m^2 for placebo. Patients with moderate renal impairment at baseline had larger mean changes at 6 weeks (approximately 1 mL/min/1.73 m^2) with some attenuation but not a complete return to baseline by 26 weeks. These changes were observed to reverse after treatment discontinuation.

Increases in low-density lipoprotein cholesterol (LDL-C)
In the pool of three placebo-controlled trials, dose-related increases in LDL-C were observed in patients treated with ertugliflozin. Mean percent changes from baseline in LDL-C relative to placebo were 2.6% and 5.4% with ertugliflozin 5 mg and ertugliflozin 15 mg, respectively. The range of mean baseline LDL-C was 2.50 to 2.53 mmol/L across treatment groups.

Increases in haemoglobin
In the pool of three placebo-controlled trials, mean changes (percent changes) from baseline in haemoglobin were 4.6 g/L (3.5%) with ertugliflozin 5 mg, 4.8 g/L (3.5%) with ertugliflozin 15 mg, and -2.1 g/L (-1.4%) with placebo. The range of mean baseline haemoglobin was 139.0 to 140.0 g/L across treatment groups. At the end of treatment, 0.2%, 0.4%, and 0.0% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively, had a haemoglobin increase greater than 20 g/L and above the upper limit of normal. This change in laboratory parameter is of unknown clinical significance.

Increases in serum phosphate
In the pool of three placebo-controlled trials, mean changes (percent changes) from baseline in serum phosphate were 0.07 mmol/L (6.8%) with STEGLATRO 5 mg, 0.08 mmol/L (8.5%) with STEGLATRO 15 mg, and 0.01 mmol/L (1.9%) with placebo. The mean baseline serum phosphate was 1.14 mmol/L across treatment groups. In a clinical trial of patients with moderate renal impairment, mean changes (percent changes) from baseline at Week 26 in serum phosphate were 0.09 mmol/L (9.7%) with STEGLATRO 5 mg, 0.08 mmol/L (7.8%) with STEGLATRO 15 mg, and -0.00 mmol/L (0.8%) with placebo. This change in laboratory parameter is of unknown clinical significance.

Sitagliptin phosphate
The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin 100 mg compared to patients treated with placebo. Across clinical studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs. placebo; mean baseline WBC approximately 6,600 cells/microL) was observed due to an increase in neutrophils. This observation was seen in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant.

Adverse reactions in specific populations

Elderly patients

Ertugliflozin
Across the clinical program, a total of 876 (25.7%) patients treated with ertugliflozin were 65 years and older, and 152 (4.5%) patients treated with ertugliflozin were 75 years and older. Patients 65 years and older had a higher incidence of adverse reactions related to volume depletion compared to younger patients; events were reported in 2.2%, 2.6%, and 1.1% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and comparator, respectively [see 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Renal impairment

Ertugliflozin
The efficacy and safety of ertugliflozin were evaluated in a study of patients with moderate renal impairment. In this study, 202 patients exposed to ertugliflozin had an eGFR between 45 and 60 mL/min/1.73 m^2 and 111 patients exposed to ertugliflozin had an eGFR between 30 and 45 mL/min/1.73 m^2. The glucose-lowering efficacy of ertugliflozin decreased in patients with worsening renal function. Compared to placebo-treated patients, patients with moderate renal impairment treated with ertugliflozin had increases in serum creatinine and decreases in eGFR, and increased risks for renal-related and volume depletion adverse reactions [see 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Postmarketing experience:

The following adverse reactions have been identified during post-approval use. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Ertugliflozin
Infections and infestations – Necrotising fasciitis of the perineum (Fournier's Gangrene) [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.]

Sitagliptin
Additional adverse reactions have been identified during postmarketing use of sitagliptin as monotherapy and/or in combination with other antihyperglycaemic agents.
Infections and infestations: upper respiratory tract infection; nasopharyngitis
Nervous system disorders: headache
Gastrointestinal disorders: acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Pancreatitis]; constipation; vomiting
Musculoskeletal and connective tissue disorders: arthralgia; myalgia; pain in extremity; back pain
Renal and urinary disorders: worsening renal function, including acute renal failure (sometimes requiring dialysis)
Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, pruritus, bullous pemphigoid [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Bullous pemphigoid], and exfoliative skin conditions, including

Stevens-Johnson syndrome have been reported with use of sitagliptin [see 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Hypersensitivity reactions].

Reporting suspected adverse reactions
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

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

In the event of an overdose, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring including obtaining an electrocardiogram, and institute supportive treatment) as dictated by the patient's clinical status.

Ertugliflozin
Ertugliflozin did not show any toxicity in healthy subjects at single oral doses up to 300 mg and multiple doses up to 100 mg daily for 2 weeks. No potential acute symptoms and signs of overdose were identified.

Removal of ertugliflozin by haemodialysis has not been studied.

Sitagliptin
During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin [see 5.1 PHARMACODYNAMIC PROPERTIES]. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4 hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

STEGLUJAN
STEGLUJAN combines two antihyperglycaemic agents with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: ertugliflozin, a SGLT2 inhibitor, and sitagliptin phosphate, a DPP-4 inhibitor.

Ertugliflozin
SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Patients with diabetes have been shown to have elevated reabsorption of glucose which may result in persistence of hyperglycaemia. Ertugliflozin is an inhibitor of SGLT2 with an IC_{50} of 0.88 nM. It displays >2,200-fold selectivity for SGLT2 over SGLT1 (responsible for glucose absorption in the gut). By inhibiting SGLT2, ertugliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion (UGE), which lowers fasting plasma glucose (FPG) and haemoglobin $A1_C$ levels in an insulin-independent manner. Additionally, UGE results in caloric loss and with ensuing weight loss. Ertugliflozin also causes an osmotic diuresis, which may result in reduction of blood pressure. UGE is observed after the first dose. UGE with ertugliflozin depends on plasma glucose levels and glomerular filtration rate. Consequently, UGE is reduced as plasma glucose levels fall, which reduces the risk of hypoglycaemia.

Sitagliptin phosphate
Sitagliptin is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycaemic control in patients with type 2 diabetes by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiological regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signalling pathways involving cyclic AMP. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose-dependent. When blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin secretion is markedly enhanced as glucose rises above normal concentrations. GLP-1 does not impair the normal glucagon response to hypoglycaemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyses the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. This glucose-dependent mechanism is unlike the mechanism seen with sulfonylureas where insulin is released even when glucose levels are low, which can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects. In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A1c (HbA1c) and lower fasting and postprandial glucose concentrations. Sitagliptin inhibits DPP-4 with nanomolar potency (IC_{50} 18 nM). It does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Inhibition of DPP-8 or DPP-9 is associated with toxicity in preclinical animal models and alteration of immune function *in vitro*.

Ertugliflozin

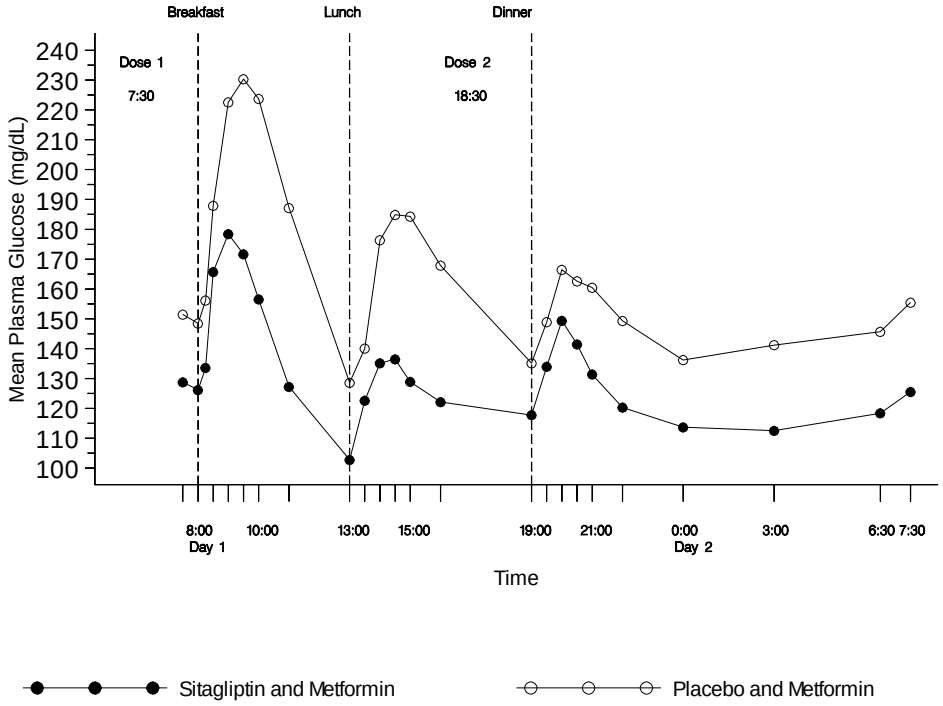
Urinary glucose excretion and urinary volume
Dose-dependent increases in the amount of glucose excreted in urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following single- and multiple-dose administration of ertugliflozin. Dose-response modelling indicates that ertugliflozin 5 mg and 15 mg result in near maximal urinary glucose excretion (UGE), with the 15 mg dose providing incrementally greater UGE relative to the 5 mg dose. Enhanced UGE is maintained after multiple-dose administration. UGE with ertugliflozin also results in increases in urinary volume. Ertugliflozin acts independently of insulin secretion and insulin action. Over time, significant improvement in beta cell function (HOMA-beta) has been observed in clinical studies with ertugliflozin.

Cardiac electrophysiology
In a randomised, placebo-controlled, active-comparator, crossover study, 42 healthy subjects were administered a single oral supratherapeutic dose of ertugliflozin 100 mg (6.7 times the maximum recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with 100 mg ertugliflozin.

Sitagliptin
In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24-hour period, resulting in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose excursion following an oral glucose load or a meal.

In a study of patients with type 2 diabetes inadequately controlled on metformin monotherapy, glucose levels monitored throughout the day were significantly lower in patients who received sitagliptin 100 mg per day (50 mg twice daily) in combination with metformin compared with patients who received placebo with metformin (see Figure 3).

Figure 3: 24-hour Plasma Glucose Profile after 4-Week Treatment with Sitagliptin 50 mg BID with Metformin or Placebo with Metformin



In Phase III clinical studies of 18- and 24-week duration, treatment with sitagliptin 100 mg daily in patients with type 2 diabetes significantly improved beta cell function, as assessed by several markers, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. There are no clinical studies that demonstrate that sitagliptin alters the natural history of impaired glucose tolerance or type 2 diabetes mellitus. The durability of efficacy requires further study.

In Phase II studies, sitagliptin 50 mg twice daily provided no additional glycaemic efficacy compared to sitagliptin 100 mg once daily.

In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycaemia, suggesting that the insulinotropic and glucagon suppressive actions of the drug are glucose dependent.

Effects on blood pressure

In a randomised, placebo-controlled crossover study in hypertensive patients on one or more anti-hypertensive drugs (including angiotensin-converting enzyme inhibitors, angiotensin-II antagonists, calcium-channel blockers, beta-blockers and diuretics), coadministration with sitagliptin was generally well tolerated. In these patients, sitagliptin had a modest blood pressure lowering effect; 100 mg per day of sitagliptin reduced 24-hour mean ambulatory systolic blood pressure by approximately 2 mmHg, as compared to placebo. Reductions have not been observed in subjects with normal blood pressure.

Cardiac electrophysiology

In a randomised, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and

placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline at 3 hours postdose was 8.0 msec. This small increase was not considered to be clinically significant. At the 800-mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100 mg dose.

In patients with type 2 diabetes administered sitagliptin 100 mg (N = 81) or sitagliptin 200 mg (N = 63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

Clinical trials

Glycaemic control trials in patients with type 2 diabetes

The efficacy and safety of ertugliflozin in combination with sitagliptin have been studied in 3 multicentre, randomised, double-blind, placebo- and active comparator-controlled, Phase 3 clinical studies involving 1,985 patients with type 2 diabetes. These studies included White, Hispanic, Black, Asian, and other racial and ethnic groups, and patients with an age range of 21 to 85 years.

In patients with type 2 diabetes, treatment with ertugliflozin in combination with sitagliptin produced clinically and statistically significant improvements in HbA1c and fasting plasma glucose (FPG) compared to placebo or active comparator.

In patients with type 2 diabetes treated with ertugliflozin in combination with sitagliptin the improvement in HbA1c was generally similar across subgroups defined by age, sex, and race.

None of these clinical studies used the ertugliflozin+sitagliptin FDC tablets; however bioequivalence of STEGLUJAN with coadministered ertugliflozin and sitagliptin tablets was demonstrated for all tablet strengths.

Factorial study with ertugliflozin and sitagliptin (JANUVIA) as add-on combination therapy with metformin

A total of 1,233 patients with type 2 diabetes participated in a randomised, double-blind, multi-centre, 26-week, active-controlled study to evaluate the efficacy and safety of ertugliflozin 5 mg or 15 mg in combination with JANUVIA 100 mg compared to the individual components. Patients with type 2 diabetes inadequately controlled on metformin monotherapy (≥1,500 mg/day) were randomised to one of five active-treatment arms: ertugliflozin 5 mg or 15 mg, JANUVIA 100 mg, or JANUVIA 100 mg in combination with 5 mg or 15 mg ertugliflozin administered once daily in addition to continuation of background metformin therapy.

At Week 26, ertugliflozin 5 mg or 15 mg used in combination with JANUVIA 100 mg provided statistically significant improvement in HbA1c and FPG compared to the individual components (see Table 6 and Figure 4). More patients receiving ertugliflozin 5 mg or 15 mg in combination with JANUVIA 100 mg achieved an HbA1c <7% compared to the individual components. Treatment with ertugliflozin 5 mg or 15 mg in combination with JANUVIA 100 mg also resulted in a statistically significant reduction in body weight and systolic blood pressure compared to JANUVIA 100 mg.

Table 6: Results at Week 26 from a Factorial Study with Ertugliflozin and Sitagliptin as Add-on Combination Therapy with Metformin Compared to Individual Components Alone*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Sitagliptin 100 mg	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg
HbA1c (%)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	8.57	8.57	8.50	8.56	8.56
Change from baseline (LS mean†)	-1.02	-1.08	-1.05	-1.49	-1.52
Difference from Sitagliptin Ertugliflozin 5 mg Ertugliflozin 15 mg (LS mean†, 95% CI)				-0.43‡ (-0.60, -0.27) -0.46‡ (-0.63, -0.30)	-0.47‡ (-0.63, -0.30) -0.44‡ (-0.61, -0.27)
Patients [N (%)] with HbA1c <7%	66 (26.4)	79 (31.9)	81 (32.8)	127 (52.3)§	120 (49.2)§
FPG (mmol/L)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	10.22	9.96	9.85	10.20	9.83
Change from baseline (LS mean†)	-1.98	-2.05	-1.42	-2.44	-2.70
Difference from Sitagliptin Ertugliflozin 5 mg Ertugliflozin 15 mg (LS mean†, 95% CI)				-1.02‡ (-1.33, -0.71) - 0.46¶ (-0.77, -0.15)	-1.28‡ (-1.60, -0.97) -0.65‡ (-0.96, -0.35)
Body Weight (kg)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	88.6	88.0	89.8	89.5	87.5
Change from baseline (LS mean†)	-2.7	-3.7	-0.7	-2.5	-2.9
Difference from Sitagliptin (LS mean†, 95% CI)				-1.8‡ (-2.5, -1.2)	-2.3‡ (-2.9, -1.6)
Systolic Blood Pressure (mmHg)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	129.7	128.9	128.3	130.2	129.1
Change from baseline (LS mean†)	-3.9	-3.7	-0.7	-3.4	-3.7
Difference from Sitagliptin (LS mean†, 95% CI)				-2.8¶ (-4.7, -0.8)	-3.0¶ (-4.9, -1.1)
Efficacy in patients with high baseline HbA1c (≥10%)					
HbA1c (%)	**N = 25**	**N = 21**	**N = 26**	**N = 20**	**N = 22**
Baseline (mean)	10.66	10.51	10.46	10.46	10.39
Change from baseline (LS mean#)	-2.10	-1.30	-1.82	-2.35	-2.66
Difference from Sitagliptin Ertugliflozin 5 mg Ertugliflozin 15 mg (LS mean#, 95% CI)				-0.53 (-1.08, -0.03) -0.24 (-0.80, -0.32)	-0.84 (-1.38, -0.30) -1.36 (-1.91, -0.81)

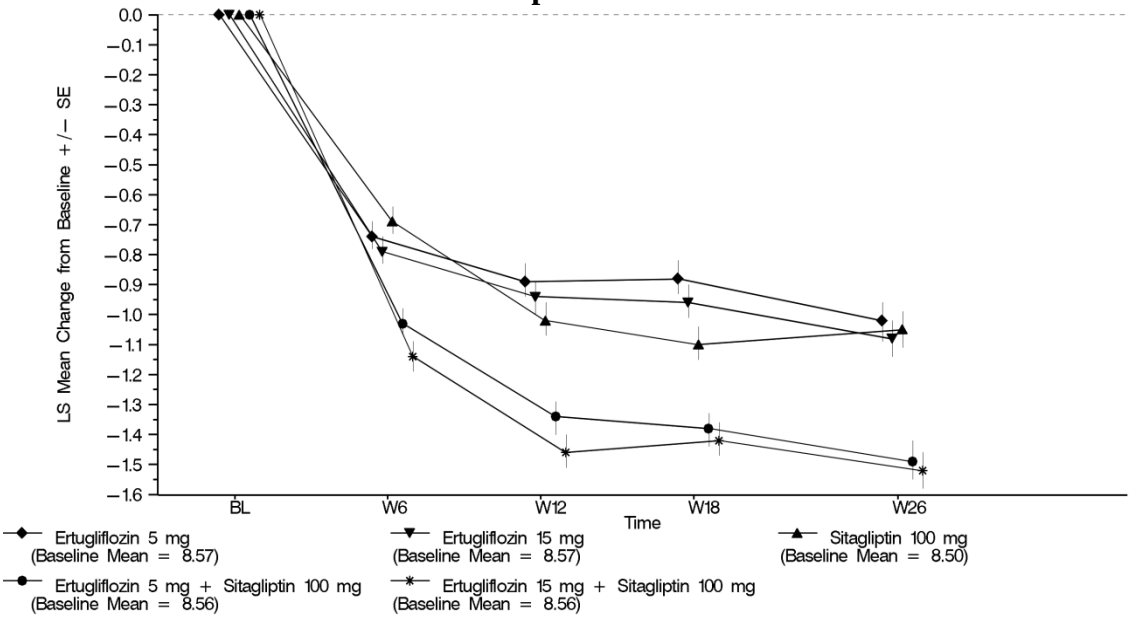
* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for time, baseline eGFR and the interaction of time by treatment.
‡ p<0.001 compared to control group.

§ $p<0.001$ compared to corresponding dose of ertugliflozin or sitagliptin (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

¶ $p\leq0.005$ compared to control group.

Obtained from a repeated measures ANCOVA model adjusted for baseline eGFR, baseline HbA1c, treatment, subgroup, treatment-by-subgroup, and treatment-by-time-by-subgroup interactions.

Figure 4: HbA1c (%) Change over Time in a Factorial Study with Ertugliflozin and Sitagliptin as Add-on Combination Therapy with Metformin Compared to Individual Components Alone*



* Based on the full analysis set population, which included all randomised, treated patients with at least one HbA1c measurement.

Ertugliflozin as add-on combination therapy with metformin and sitagliptin (JANUVIA)

A total of 463 patients, with type 2 diabetes inadequately controlled on metformin (≥1,500 mg/day) and JANUVIA 100 mg once daily participated in a randomised, double-blind, multi-centre, 26-week, placebo-controlled study to evaluate the efficacy and safety of ertugliflozin. Patients were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo administered once daily in addition to continuation of background metformin and JANUVIA therapy.

At Week 26, treatment with ertugliflozin at 5 mg or 15 mg daily provided statistically significant improvements in HbA1c, FPG, body weight, and systolic blood pressure compared to placebo. Ertugliflozin also resulted in a greater proportion of patients achieving an HbA1c <7% compared to placebo (see Table 7).

Table 7: Results at Week 26 from an Add-on Study of Ertugliflozin in Combination with Metformin and Sitagliptin*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
HbA1c (%)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	8.05	8.00	8.03
Change from baseline (LS mean†)	-0.78	-0.86	-0.09
Difference from placebo (LS mean†, 95% CI)	-0.69‡ (-0.87, -0.50)	-0.76‡ (-0.95, -0.58)	
Patients [N (%)] with HbA1c <7%	50 (32.1) §	61 (39.9) §	26 (17.0)
FPG (mmol/L)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	9.31	9.53	9.41
Change from baseline (LS mean†)	-1.49	-1.83	-0.10§
Difference from placebo (LS mean†, 95% CI)	-1.40‡ (-1.82, -0.97)	-1.74‡ (-2.16, -1.31)	
Body Weight (kg)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	87.6	86.6	86.5
Change from baseline (LS mean†)	-3.3	-3.0	-1.3
Difference from placebo (LS mean†, 95% CI)	-2.0‡ (-2.6, -1.4)	-1.7‡ (-2.3, -1.1)	
Systolic Blood Pressure (mmHg)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	132.1	131.6	130.2
Change from baseline (LS mean†)	-3.8	-4.8	-0.9
Difference from placebo (LS mean†, 95% CI)	-2.9¶ (-5.4, -0.5)	-3.9¶ (-6.4, -1.5)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for time, prior antihyperglycaemic medication, baseline eGFR, and the interaction of time by treatment.
‡ p<0.001 compared to placebo.
§ p<0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).
¶ p<0.05 compared to placebo.

Initial combination therapy of ertugliflozin and sitagliptin (JANUVIA)
A total of 291 patients with type 2 diabetes inadequately controlled on diet and exercise participated in a randomised, double-blind, multi-centre, placebo-controlled 26-week study to evaluate the efficacy and safety of ertugliflozin in combination with JANUVIA. These patients, who were not receiving any background anti-hyperglycaemic treatment, were randomised to ertugliflozin 5 mg or ertugliflozin 15 mg in combination with JANUVIA (100 mg) or placebo, once daily.

At Week 26, treatment with ertugliflozin 5 mg and 15 mg in combination with JANUVIA at 100 mg daily provided significant improvements in HbA1c, FPG, 2-hour post-prandial glucose (PPG), body weight, and systolic blood pressure compared to placebo. Ertugliflozin 5 mg and 15 mg in combination with JANUVIA at 100 mg daily also resulted in a significantly higher proportion of patients achieving an HbA1c <7% compared with placebo (see Table 8).

Table 8: Results at Week-26 from an Initial Combination Therapy Study of Ertugliflozin and Sitagliptin*

	Ertugliflozin 5 mg + Sitagliptin	Ertugliflozin 15 mg + Sitagliptin	Placebo
HbA1c (%)	**N = 98**	**N = 96**	**N = 96**
Baseline (mean)	8.90	8.98	8.95
Change from baseline (LS mean†)	-1.60	-1.68	-0.44
Difference from placebo (LS mean† and 95% CI)	-1.16‡ (-1.49, -0.84)	-1.24‡ (-1.57, -0.91)	
Patients [N (%)] with HbA1c <7%	35 (35.7)§	30 (31.3)§	8 (8.3)
FPG (mmol/L)	**N = 98**	**N = 96**	**N = 96**
Baseline (mean)	10.99	10.42	11.52
Change from baseline (LS mean†)	- 2.68	- 3.07	- 0.52
Difference from placebo (LS mean†, 95% CI)	-2.16‡ (-2.77, -1.55)	-2.56‡ (-3.17, -1.94)	
2-hour PPG (mmol/L)	**N = 97**	**N = 95**	**N = 91**
Baseline (mean)	15.61	15.63	15.95
Change from baseline (LS mean†)	-4.60	-5.00	-1.13
Difference from placebo (LS mean†, 95% CI)	-3.46‡ (-4.47, -2.46)	-3.87‡ (-4.87, -2.86)	
Body Weight (kg)	**N = 98**	**N = 96**	**N = 97**
Baseline (mean)	90.8	91.3	95.0
Change from baseline (LS mean†)	-2.9	-3.0	-0.9
Difference from placebo (LS mean†, 95% CI)	-2.0‡ (-3.0, -1.0)	-2.1‡ (-3.1, -1.1)	
Systolic Blood Pressure (mmHg)	**N = 98**	**N = 96**	**N = 97**
Baseline (mean)	130.7	129.2	127.4
Change from baseline (LS mean†)	-2.0	-4.0	2.4
Difference from placebo (LS mean†, 95% CI)	-4.4¶ (-7.9, -1.0)	-6.4‡ (-9.8, -3.0)	

* N includes all patients who received at least one dose of study medication and had at least one measurement of the outcome variable.
† Least squares means adjusted for time, prior antihyperglycaemic medication , baseline eGFR, and the interaction of time by treatment.
‡ p<0.001 compared to placebo.
§ p<0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).
¶ p = 0.011 compared to placebo.

Cardiovascular outcomes studies

Ertugliflozin

VERTIS CV study
The effect of ertugliflozin on cardiovascular risk in adult patients with type 2 diabetes and established atherosclerotic cardiovascular disease was evaluated in the VERTIS CV study, a multicentre, multi-national, randomised, double-blind, placebo-controlled, event-driven trial. The study compared the risk of experiencing a major adverse cardiovascular event (MACE) between ertugliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease.

A total of 8246 patients were randomized (ertugliflozin 5 mg N = 2752, ertugliflozin 15 mg N = 2747, or placebo N =2747) and followed for a median of 3 years. Approximately 88% of the

study population was Caucasian, 6% was Asian, and 3% was Black. The mean age was 64 years and approximately 70% were male.

All patients in the study had inadequately controlled type 2 diabetes mellitus at baseline (HbA1c greater than or equal to 7%). The mean duration of type 2 diabetes mellitus was 13 years, the mean HbA1c at baseline was 8.2% and the mean eGFR was 76 mL/min/1.73 m^2. At baseline, patients were treated with one (32%) or more (67%) antidiabetic medications including metformin (76%), insulin (47%), sulfonylureas (41%), DPP-4 inhibitors (11%) and GLP-1 receptor agonists (3%).

Almost all patients (99%) had established atherosclerotic cardiovascular disease at baseline including: a documented history of coronary artery disease (76%), cerebrovascular disease (23%) or peripheral artery disease (19%). Approximately 24% patients had a history of heart failure (HF). At baseline, the mean systolic blood pressure was 133 mmHg, the mean diastolic blood pressure was 77 mmHg, the mean LDL was 2.3 mmol/L, and the mean HDL was 1.1 mmol/L. At baseline, approximately 81% of patients were treated with renin angiotensin system inhibitors, 69% with beta-blockers, 43% with diuretics, 82% with statins, 4% with ezetimibe, and 89% with antiplatelet agents.

The primary endpoint in VERTIS CV was the time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event was defined as occurrence of either a cardiovascular death or a nonfatal myocardial infarction (MI) or a nonfatal stroke. The statistical analysis plan pre-specified that the 5 and 15 mg doses would be combined for the analysis. A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE. Type-1 error was controlled across multiple tests using a hierarchical testing strategy.

The incidence rate of MACE was similar between the ertugliflozin-treated and placebo-treated patients. The estimated hazard ratio of MACE associated with ertugliflozin relative to placebo was 0.97 with 95.6% confidence interval (0.85, 1.11). The upper bound of this confidence interval, 1.11, excluded a risk larger than 1.3 (Table 9). Results for the individual 5 mg and 15 mg doses were consistent with results for the combined dose group.

Table 9: Analysis of MACE and its Components from the VERTIS CV Study*

Endpoint†	Placebo (N = 2747)		Ertugliflozin (N = 5499)		Hazard Ratio vs Placebo (CI) ‡
	N (%)	Event Rate (per 100 person-years)	N (%)	Event Rate (per 100 person-years)	
MACE (CV death, non-fatal MI, or non-fatal stroke)	327 (11.9)	4.0	653 (11.9)	3.9	0.97 (0.85, 1.11)
Non-fatal MI	148 (5.4)	1.6	310 (5.6)	1.7	1.04 (0.86, 1.27)
Non-fatal Stroke	78 (2.8)	0.8	157 (2.9)	0.8	1.00 (0.76, 1.32)
CV death	184 (6.7)	1.9	341 (6.2)	1.8	0.92 (0.77, 1.11)

N = Number of patients, CI = Confidence interval, CV = Cardiovascular, MI = Myocardial infarction.

* Intent-to-treat analysis set.

† MACE was evaluated in subjects who took at least one dose of study medication and, for subjects who discontinued study medication prior to the end of the study, censored events that occurred more than 365 days after the last dose of study medication. Other endpoints were evaluated using all randomized subjects and events that occurred any time after the first dose of study medication until the last contact date. The total number of first events was analyzed for each endpoint.

‡ For MACE a 95.6% CI is presented, for other endpoints a 95% CI is presented.

Sitagliptin (JANUVIA)

TECOS study

The Trial Evaluating Cardiovascular Outcomes with JANUVIA (TECOS) was a randomised study in 14,671 patients in the intention-to-treat population with an HbA1c of ≥6.5 to 8.0% with established CV disease who received JANUVIA (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥30 and <50 mL/min/1.73 m^2) or placebo (7,339) added to usual care targeting regional standards for HbA1c and CV risk factors. Patients with an eGFR <30 mL/min/1.73 m^2 were not to be enrolled in the study. The study population included 2,004 patients ≥75 years of age and 3,324 patients with renal impairment (eGFR <60 mL/min/1.73 m^2).

Over the course of the study, the overall estimated mean (SD) difference in HbA1c between the JANUVIA and placebo groups was 0.29% (0.01), 95% CI (-0.32, -0.27); p<0.001.

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; first occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.

After a median follow up of 3 years, JANUVIA, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalization for heart failure compared to usual care without JANUVIA in patients with type 2 diabetes (Table 10). There have been no clinical studies establishing macrovascular risk reduction with ertugliflozin.

Table 10: Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	Sitagliptin 100 mg		Placebo		Hazard Ratio (95% CI)	p-value†
	N (%)	Incidence Rate per 100 Patient-Years*	N (%)	Incidence Rate per 100 Patient-Years*		
Analysis in the Intention-to-Treat Population						
Number of Patients	7,332		7,339			
Primary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2	0.98 (0.89–1.08)	<0.001
Secondary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)	745 (10.2)	3.6	746 (10.2)	3.6	0.99 (0.89–1.10)	<0.001
Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89-1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81–1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79–1.19)	0.760
Hospitalisation for unstable angina	116 (1.6)	0.5	129 (1.8)	0.6	0.90 (0.70–1.16)	0.419
Death from any cause	547 (7.5)	2.5	537 (7.3)	2.5	1.01 (0.90–1.14)	0.875
Hospitalisation for heart failure‡	228 (3.1)	1.1	229 (3.1)	1.1	1.00 (0.83–1.20)	0.983

* Incidence rate per 100 patient-years is calculated as 100 × (total number of patients with ≥1 event during eligible exposure period per total patient-years of follow-up).

† Based on a Cox model stratified by region.

- For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard ratio is less than 1.3.
- For all other endpoints, the p-values correspond to a test of differences in hazard rates.

‡ The analysis of hospitalisation for heart failure was adjusted for a history of heart failure at baseline.

5.2 PHARMACOKINETIC PROPERTIES

STEGLUJAN

STEGLUJAN has been shown to be bioequivalent to coadministration of corresponding doses of ertugliflozin and sitagliptin tablets.

Ertugliflozin

The pharmacokinetics of ertugliflozin are similar in healthy subjects and patients with type 2 diabetes. The steady-state mean plasma area under the curve (AUC) and peak concentration (C_{max}) were 398 ng.hr/mL and 81.3 ng/mL, respectively, with 5 mg ertugliflozin once daily treatment, and 1,193 ng.hr/mL and 268 ng/mL, respectively, with 15 mg ertugliflozin once daily treatment. Steady-state is reached after 4 to 6 days of once-daily dosing with ertugliflozin. Ertugliflozin does not exhibit time-dependent pharmacokinetics and accumulates in plasma up to 10-40% following multiple dosing.

Sitagliptin
The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100-mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption

STEGLUJAN
The effects of a high-fat meal on the pharmacokinetics of ertugliflozin and sitagliptin when administered as STEGLUJAN tablets are comparable to those reported for the individual tablets. Administration of STEGLUJAN with food decreased ertugliflozin C_{max} by 29% and had no meaningful effect on ertugliflozin AUC_{inf}, or on sitagliptin AUC_{inf} and C_{max}.

Ertugliflozin
Following single-dose oral administration of 5 mg and 15 mg of ertugliflozin, peak plasma concentrations (median T_{max}) of ertugliflozin occur at 1 hour postdose under fasted conditions. Plasma C_{max} and AUC of ertugliflozin increase in a dose-proportional manner following single doses from 0.5 mg to 300 mg and following multiple doses from 1 mg to 100 mg. The absolute oral bioavailability of ertugliflozin following administration of a 15-mg dose is approximately 100%.

Administration of ertugliflozin with a high-fat and high-calorie meal decreases ertugliflozin C_{max} by 29% and prolongs T_{max} by 1 hour, but does not alter AUC as compared with the fasted state. The observed effect of food on ertugliflozin pharmacokinetics is not considered clinically relevant, and ertugliflozin may be administered with or without food. In Phase 3 clinical trials, Ertugliflozin was administered without regard to meals.

Sitagliptin phosphate
The absolute bioavailability of sitagliptin is approximately 87%. Coadministration of a high-fat meal with sitagliptin phosphate had no effect on the pharmacokinetics of sitagliptin.

Distribution

Ertugliflozin
The mean steady-state volume of distribution of ertugliflozin following an intravenous dose is 85.5 L. Plasma protein binding of ertugliflozin is 93.6% and is independent of ertugliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood-to-plasma concentration ratio of ertugliflozin is 0.66.

Sitagliptin phosphate
The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 L. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Metabolism

Ertugliflozin
Metabolism is the primary clearance mechanism for ertugliflozin. The major metabolic pathway for ertugliflozin is UGT1A9 and UGT2B7-mediated O-glucuronidation to two glucuronides. These are present in plasma at levels 2- and 4-times lower than ertugliflozin and are pharmacologically inactive at clinically relevant concentrations. CYP-mediated (oxidative) metabolism of ertugliflozin is minimal (12%).

Sitagliptin phosphate
Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine.

Following a [^{14}C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Excretion

Ertugliflozin
The mean systemic plasma clearance following an intravenous 100 µg dose was 11.2 L/hr. The mean elimination half-life in type 2 diabetic patients with normal renal function was estimated to be 16.6 hours based on the population pharmacokinetic analysis. Following administration of an oral [^{14}C] ertugliflozin solution to healthy subjects, approximately 40.9% and 50.2% of the drug-related radioactivity was eliminated in faeces and urine, respectively. Only 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and 33.8% as unchanged ertugliflozin in faeces, which is likely due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent.

Sitagliptin
Following administration of an oral [^{14}C]-sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in faeces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p- glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Special Populations

Renal impairment

STEGLUJAN
Studies characterising the pharmacokinetics of ertugliflozin and sitagliptin after administration of STEGLUJAN in renally impaired patients have not been performed [see 4.2 DOSE AND METHOD OF ADMINISTRATION].

Ertugliflozin
In a Phase 1 clinical pharmacology study in patients with type 2 diabetes and mild, moderate, or severe renal impairment (as determined by estimated glomerular filtration rate (eGFR), following a single-dose administration of 15 mg ertugliflozin, the mean increases in AUC of ertugliflozin were ≤1.7-fold, compared to subjects with normal renal function. These increases in ertugliflozin AUC are not considered clinically relevant. There were no clinically meaningful differences in the ertugliflozin C_{max} values among the different renal function groups. The 24-hour urinary glucose excretion declined with increasing severity of renal impairment. The plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.

Sitagliptin phosphate
An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency, and an approximately 4-fold increase was observed in patients with severe renal insufficiency and in patients with end-stage renal disease (ESRD) on haemodialysis, as compared to normal healthy control subjects.

Hepatic impairment

Ertugliflozin
Moderate hepatic impairment (based on the Child-Pugh classification) did not result in an increase in exposure of ertugliflozin. The AUC of ertugliflozin decreased by approximately 13%, and C_{max} decreased by approximately 21% compared to subjects with normal hepatic function. This decrease in ertugliflozin exposure is not considered clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment. The plasma protein binding of ertugliflozin was unaffected in patients with moderate hepatic impairment.

Sitagliptin phosphate
In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of sitagliptin phosphate. These differences are not considered to be clinically meaningful.

There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score >9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

Paediatric
No studies with STEGLUJAN have been performed in paediatric patients.

Effects of age, body weight, gender, and race

Ertugliflozin
Based on a population pharmacokinetic analysis, age, body weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin.

Sitagliptin
Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Body mass index (BMI) had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data, including subjects of White, Hispanic, Black, Asian, and other racial groups.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ertugliflozin
Ertugliflozin was not mutagenic in the bacterial reverse mutation assay, and was not clastogenic *in vitro* (cytogenetic assay in human lymphocytes), or *in vivo* rat bone marrow micronucleus test.

Sitagliptin phosphate
Sitagliptin was not mutagenic or clastogenic in a battery of genetic toxicology studies, including the Ames bacterial assay (microbial mutagenesis test), Chinese hamster ovary cells (CHO cells) chromosome aberration assay, an *in vitro* cytogenetics assay using CHO cells, an *in vitro* rat hepatocyte DNA alkaline elution assay (an assay which measures the compound's ability to induce single strand breaks in DNA), and an *in vivo* micronucleus assay.

Carcinogenicity

No carcinogenicity studies have been conducted with ertugliflozin and sitagliptin in combination.

Ertugliflozin
The carcinogenic potential of ertugliflozin was examined in 2-year studies in mice and rats. Administration was by oral gavage. There were no ertugliflozin-related neoplastic findings in mice at doses up to 40 mg/kg/day (approximately 41 times human exposure at the MRHD of 15 mg/day based on plasma AUC for unbound ertugliflozin) or in female rats at doses up to 15

mg/kg/day (approximately 50 times human exposure), the highest dose levels tested. In male rats, treatment with ertugliflozin at 15 mg/kg/day increased the incidence of benign adrenal medullary phaeochromocytoma. This finding was attributed to carbohydrate malabsorption leading to altered calcium homeostasis and is not considered relevant to human risk. The no-observed-effect level (NOEL) for neoplasia in male rats was 5 mg/kg/day (approximately 13 times human exposure at the MRHD of 15 mg/day) and no neoplasia was observed in female rats.

Sitagliptin phosphate
A two-year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of hepatic adenomas and carcinomas in the high-dose males and hepatic carcinomas in the high-dose females. This dose in rats results in approximately 58 times the human exposure based on the recommended daily adult human dose of 100 mg/day. This dose level was associated with hepatotoxicity in rats. The no-observed effect level for induction of hepatic neoplasia was 150 mg/kg/day, approximately 19-fold the human exposure at the 100-mg recommended dose. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. The clinical significance of these findings for humans is unknown.

In a two-year carcinogenicity study conducted in mice, sitagliptin did not increase tumour incidence at oral doses up to 500 mg/kg/day (approximately 68 times the human exposure at the recommended daily adult human dose of 100 mg/day).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each film-coated tablet of STEGLUJAN contains the following inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate, croscarmellose sodium, sodium stearyl fumarate, magnesium stearate, and carnauba wax.

The film coating contains: hypromellose, hyprolose, titanium dioxide, iron oxide red, iron oxide black, and iron oxide yellow.

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 30ºC. Store in original packaging.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in aluminium/aluminium blister packs of 7 tablets (starter pack) and 28 tablets.

Not all presentations may be supplied.

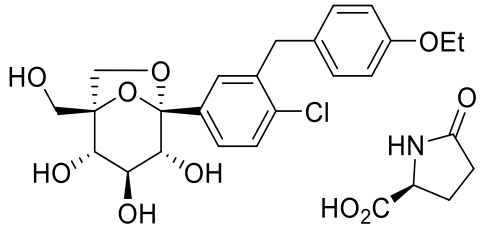
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

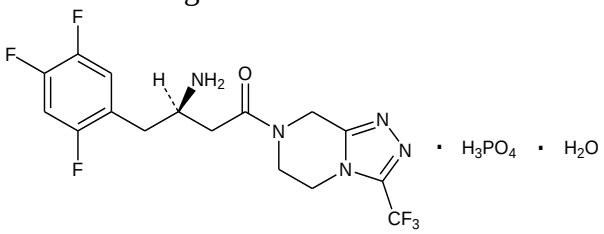
Chemical structure

Ertugliflozin
The chemical name of ertugliflozin pyroglutamic acid is (1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2*S*)-5-oxopyrrolidine-2-carboxylic acid. The molecular formula is $C_{27}H_{32}ClNO_{10}$ and the molecular weight is 566.00. The chemical structure is:



Ertugliflozin pyroglutamic acid is a white to off-white powder that is soluble in ethyl alcohol and acetone, slightly soluble in ethyl acetate and acetonitrile and very slightly soluble in water.

Sitagliptin phosphate
The chemical name of sitagliptin phosphate is 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate. The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32. The structural formula is:



Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

CAS number

Ertugliflozin
The CAS Registry Number is 1210344-83-4.

Sitagliptin phosphate
The CAS Registry Number is 654671-78-0.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4)

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Rd
Macquarie Park NSW 2113
www.msd-australia.com.au

9 DATE OF FIRST APPROVAL

14-May-2018

10 DATE OF REVISION

06-November-2023

Summary table of changes

Section changed	Summary of new information
4.4	Update to safety information for Necrotising fasciitis of the Perineum (Fournier's Gangrene)
4.8	Addition of Necrotising fasciitis of the Perineum (Fournier's Gangrene) to Postmarketing Experience

RCN000026203-AU