AUSTRALIAN PRODUCT INFORMATION

SIDAPVIA™ 10/100
(dapagliflozin/sitagliptin) tablets

1 NAME OF THE MEDICINE

Dapagliflozin propanediol monohydrate / sitagliptin phosphate monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg dapagliflozin as dapagliflozin propanediol monohydrate and 100 mg sitagliptin as sitagliptin phosphate monohydrate.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Film coated tablet

SIDAPVIA 10 mg/100 mg tablets are yellow, oval shaped, approximately 8 mm x 15 mm, biconvex, film-coated tablets with “F M” debossed on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SIDAPVIA is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and sitagliptin is appropriate. (See sections 4.5 Interactions with other medicines and other forms of interactions and 5.1 Pharmacodynamic properties – Clinical trials.)

SIDAPVIA should be used in combination with metformin unless contraindicated or not tolerated.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose of SIDAPVIA is one dapagliflozin 10 mg/sitagliptin 100 mg tablet taken orally once daily at any time of the day, with or without food.

The tablet is to be swallowed whole.

Special patient populations

Renal impairment

SIDAPVIA should not be used in patients with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 (see sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties). Renal function should be evaluated prior to initiation of SIDAPVIA and periodically thereafter. For patients with eGFR <45 mL/min/1.73 m^2 requiring sitagliptin dosage adjustment, the use of individual mono-components at the appropriate dose or alternative therapeutic agents should be considered.

Hepatic impairment

SIDAPVIA may be used in patients with mild to moderate hepatic impairment. SIDAPVIA should not be used in patients with severe hepatic impairment (see section 4.4 Special warnings and precautions for use).

Use in the elderly

SIDAPVIA may be used in elderly patients. However, older patients are more likely to have impaired renal function. The renal function recommendations provided for all patients also apply to elderly patients (see section 4.4 Special warnings and precautions for use).

Paediatric and adolescent

SIDAPVIA is not indicated for use in paediatric and adolescent patients. Dapagliflozin and sitagliptin have not been studied in paediatric patients under 10 years of age. Sitagliptin should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy.

4.3 CONTRAINDICATIONS

SIDAPVIA is contraindicated in patients with a history of any hypersensitivity reaction to the active substances or to any of the excipients (see sections 4.4 Special warnings and precautions for use, 4.8 Adverse effects (Undesirable effects) and 6.1 List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Use in renal impairment

SIDAPVIA should not be used in patients with an eGFR <45 mL/min/1.73 m^2. Renal function should be evaluated prior to initiation of SIDAPVIA and periodically thereafter.

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

Use in Patients at Risk for Volume depletion and or hypotension

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

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

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

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

Ketoacidosis

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

There have been reports of ketoacidosis, including DKA, a serious life-threatening condition requiring urgent hospitalisation in patients taking dapagliflozin and other sodium-glucose cotransporter 2 (SGLT2) inhibitors. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin.Patients treated with SIDAPVIA who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, SIDAPVIA should be suspended, the patient should be evaluated and prompt treatment initiated. Treatment of ketoacidosis generally requires insulin, fluid, potassium and carbohydrate replacement.

Ketoacidosis and glucosuria may be prolonged after discontinuation of SIDAPVIA in some patients, i.e. it may last longer than expected based on the plasma half-lives of dapagliflozin (see Section 5.2 Pharmacokinetic Properties). Consider monitoring for ketoacidosis and glucosuria in patients on dapagliflozin, even if drug treatment has been interrupted or discontinued.

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

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

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

Surgery

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

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

Urinary Tract Infections

There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving SGLT2 inhibitors, including dapagliflozin. Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to control in a placebo-pooled analysis up to 24 weeks (4.7% vs. 3.5%, respectively). Urinary glucose excretion may be associated with an increased risk of urinary tract infection. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (see section 4.8 Adverse effects (Undesirable effects)). Temporary interruption of SIDAPVIA

should be considered when treating pyelonephritis or urosepsis. Discontinuation of SIDAPVIA may be considered in cases of recurrent urinary tract infections; see section 4.8 Adverse effects (Undesirable effects).

Necrotising fasciitis of the perineum (Fournier's gangrene)

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

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

Lower limb amputations

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

Use with medications known to cause hypoglycaemia

Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycaemia. Hypoglycaemia has been observed when dapagliflozin or sitagliptin was used in combination with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with SIDAPVIA.

Cardiac failure

There is limited clinical experience in patients with NYHA class IV.

Hypersensitivity reactions

Post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin have been reported. 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 some reports occurring after the first dose. If a hypersensitivity reaction is suspected, SIDAPVIA should be discontinued. Other potential causes for the event should be assessed, and alternative treatment for diabetes initiated (see section 4.3 Contraindications and 4.8 Adverse effects (Undesirable effects)).

Pancreatitis

There have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis (see section 4.8 Adverse effects (Undesirable effects). 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, SIDAPVIA should be discontinued.

Arthralgia

Joint pain, which may be severe, has been reported in post-marketing reports for DPP4 inhibitors. Onset of symptoms following initiation of drug therapy may be rapid or may occur after longer periods of treatment. Discontinuation of therapy should be considered in patients who present with or experience an exacerbation of joint symptoms during treatment with DPP4 inhibitors see section 4.8 Adverse effects (Undesirable effects)).

Bullous Pemphigoid

Post-marketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP4 inhibitor use, including sitagliptin. In reported cases, patients typically responded to topical or systemic immunosuppressive treatment and discontinuation of the DPP4 inhibitor. If a patient develops blisters or erosions while receiving SIDAPVIA and bullous pemphigoid is suspected, SIDAPVIA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment (see section 4.8 Adverse effects (Undesirable effects)).

Use in hepatic impairment

There is limited experience in clinical trials in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment. SIDAPVIA should not be used in patients with severe hepatic impairment (see section 4.2 Dose and method of administration – Special Populations and section 5.2 Pharmacokinetic properties – Special Populations).

Use in the elderly

SIDAPVIA may be used in elderly patients. However, older patients may be at greater risk of volume depletion and are more likely to have impaired renal function. See section 4.2 Dose and method of administration – Special Populations and section 5.2 Pharmacokinetic properties – Special Populations).

Paediatric use

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

Delayed growth and metabolic acidosis in rats were observed in both sexes at higher doses of dapagliflozin (greater than or equal to 15 mg/kg/day). The developmental age of animals in this study approximately correlates to 2 to 16 years in humans.

Sitagliptin should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy.

Effects on laboratory tests

Dapagliflozin

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

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

Haematocrit

In the pool of 13 short-term placebo-controlled studies (see section 4.8 Adverse effects (Undesirable effects)), increases from baseline in mean haematocrit values were observed in dapagliflozin-treated patients starting at Week 1. At Week 24, the mean changes from baseline in haematocrit were -0.33% in the placebo group and 2.30% in the dapagliflozin 10 mg group. By

Week 24, haematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of dapagliflozin 10 mg-treated patients.

In the pool of 9 placebo-controlled studies with short-term and long-term data, at Week 102, the mean changes in haematocrit values were 2.68% versus -0.46%, respectively. Results for haematocrit values >55% during the short-term plus long-term phase (the majority of patients were exposed to treatment for more than one year), were similar to week 24.

Most patients with marked abnormalities of elevated haematocrit or haemoglobin had elevations measured a single time that resolved at subsequent visits.

Increased Haematocrit

Increased haematocrit has been observed with dapagliflozin treatment (see section 4.8 Adverse effects (Undesirable effects)). Patients with pronounced elevations in haematocrit should be monitored and investigated for underlying haematological disease.

Serum inorganic phosphorus

In the pool of 13 short-term placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin 10 mg-treated patients compared with placebo-treated patients (mean increases of 0.042 mmol/L *versus* -0.0013 mmol/L, respectively). Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥1.81 mmol/L for age 17-65 or ≥1.65 mmol/L for age ≥66) were reported in dapagliflozin 10 mg group *versus* placebo at Week 24 (1.7% *versus* 0.9%, respectively).

In the pool of 9 placebo-controlled studies with short-term and long-term data, at Week 102, reported increases in mean serum phosphorus were similar to week 24 results. During the short-term plus long-term phase laboratory abnormalities of hyperphosphataemia were reported in a higher proportion of patients in the dapagliflozin 10 mg group compared to placebo (3.0% *versus* 1.6%, respectively). The clinical relevance of these findings is unknown.

Lipids

In the pool of 13 short-term placebo-controlled studies, small changes from baseline in mean lipid values were reported at Week 24 in dapagliflozin 10 mg-treated patients compared with placebo-treated patients (see section 4.8 Adverse effects (Undesirable effects)). Mean percent change from baseline at Week 24 for dapagliflozin 10 mg *versus* placebo, respectively, was as follows: total cholesterol, 2.5% *versus* 0.0%; high-density lipoprotein (HDL) cholesterol, 6.0% *versus* 2.7%; low-density lipoprotein (LDL) cholesterol, 2.9% *versus* −1.0%; triglycerides, −2.7% *versus* −0.7%. The ratio between LDL cholesterol and HDL cholesterol decreased for both treatment groups at Week 24.

In the pool of 9 placebo-controlled studies with short-term and long-term data, the mean percent change from baseline at Week 102 for dapagliflozin 10 mg versus placebo, respectively, was as follows: total cholesterol, 2.1% versus −1.5%; HDL cholesterol, 6.6% versus 2.1%; LDL cholesterol, 2.9% versus −2.2%; triglycerides, −1.8% versus −1.8%.

In the cardiovascular outcome study, no clinical important differences in total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides were seen.

Liver Function Tests

In the 21-study active and placebo-controlled pool (see section 4.8 Adverse effects (Undesirable effects)), there was no imbalance across treatment groups in the incidence of elevations of ALT or AST. ALT >3 x ULN was reported in 1.2% of patients treated with dapagliflozin 10 mg and 1.6%

treated with comparator. ALT or AST >3 x ULN and bilirubin >2 x ULN was reported in 0.1% of patients on any dose of dapagliflozin, 0.2% of patients on dapagliflozin, and 0.1% of patients on comparator.

Sitagliptin

The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin 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 6600 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Dapagliflozin and sitagliptin

The lack of pharmacokinetic interaction between dapagliflozin and sitagliptin was demonstrated in a drug-drug interaction study between dapagliflozin and sitagliptin. No dose adjustment of either dapagliflozin or sitagliptin is needed when the two drugs are co-administered.

Dapagliflozin

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

In *in vitro* studies, dapagliflozin neither inhibited CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of co-administered drugs that are metabolized by these enzymes, and drugs that inhibit or induce these enzymes are not expected to alter the metabolic clearance of dapagliflozin. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the organic anion transporter-3 (OAT3) active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, organic cation transporter-2 (OCT2), OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

Effect of other drugs on dapagliflozin

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

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

Effect of dapagliflozin on other drugs

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

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

Sitagliptin

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.

Effect of other drugs on sitagliptin

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

Ertugliflozin: 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: Co-administration 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. Co-administration 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, but not restricted to, cholesterol-lowering agents (including statins, fibrates, ezetimibe), anti-platelet agents (including clopidogrel), antihypertensives (including ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (including naproxen, diclofenac, celecoxib), antidepressants (including bupropion, fluoxetine, sertraline), antihistamines (including cetirizine), proton-pump inhibitors (including omeprazole, lansoprazole), and medications for erectile dysfunction (including sildenafil).

Effect of sitagliptin on other drugs

In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, ertugliflozin, 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: Coadministration 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 glibenclamide, 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 glibenclamide, are primarily eliminated by CYP2C9.

Ertugliflozin: 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 AUCinf 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.

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 metabolised 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.

Other interactions

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Dapagliflozin/sitagliptin combination

The effect of SIDAPVIA or its mono-components on fertility in humans has not been studied. No animal fertility studies have been conducted with dapagliflozin and sitagliptin in combination.

Dapagliflozin

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

Sitagliptin

No adverse effects on fertility were observed in male and female rats given sitagliptin orally at doses up to 1000 mg/kg/day (approximately 100 times the AUC in humans at the clinical dose of 100 mg/day) prior to and throughout mating.

Use in pregnancy – Category D

Dapagliflozin/sitagliptin combination

SIDAPVIA should not be used during pregnancy. There are no adequate and well-controlled studies of SIDAPVIA or its mono-components in pregnant women. No animal embryofetal development studies have been performed with dapagliflozin and sitagliptin in combination. When pregnancy is detected, treatment with SIDAPVIA should be discontinued.

Dapagliflozin

Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, dapagliflozin must not be used during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with dapagliflozin should be discontinued.

In conventional studies of embryofetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the period of organogenesis in humans. An increased incidence of embryofetal lethality, decreased fetal weight and an increased incidence of fetal visceral and skeletal anomalies were seen in rats at maternotoxic doses (oral doses greater than or equal to 150 mg/kg/day). The no observed effect level for embryofetal effects in rats was an oral dose of 75 mg/kg/day (1530 times the exposure in patients at the maximum recommended human dose [MRHD]). No developmental toxicities were observed in rabbits at oral doses up to 180 mg/kg/day (1265 times the exposure in patients at the MRHD).

Sitagliptin

Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg/day or in rabbits given up to 125 mg/kg/day during organogenesis (up to 32 and 22 times, respectively, the AUC in humans at

the clinical dose of 100 mg/day). A slight increase in the incidence of fetal rib abnormalities (absent, hypoplastic and wavy ribs) was observed among fetuses of rats given sitagliptin at 1000 mg/kg/day (approximately 100 times the AUC in humans at 100 mg/day). Pups of rats administered sitagliptin at 1000 mg/kg/day from gestation day 6 to lactation day 20 showed reduced birth weight and postnatal body weight gain (observed prior to and after weaning). No functional or behavioural toxicity was observed in the offspring of treated rats.

Sitagliptin crosses the placenta in rats and rabbits.

Use in lactation

Dapagliflozin/sitagliptin combination

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

Dapagliflozin

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

Sitagliptin

Treatment of rats with sitagliptin during pregnancy and lactation caused decreased pup body weight gain (see Use in Pregnancy). Sitagliptin is excreted in the milk of lactating rats at a milk to plasma ratio of 4:1.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. SIDAPVIA has no anticipated or negligible influence on the ability to drive and use machines. However, when driving or operating machines, it should be taken into account that dizziness has been reported with sitagliptin. In addition, patients should be alerted to the risk of hypoglycaemia when SIDAPVIA is used in combination with insulin or an insulin secretagogue, such as a sulfonylurea.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Clinical trials

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

The safety of the combined use of 10 mg dapagliflozin and 100 mg sitagliptin has been evaluated in a placebo-controlled Phase 3 clinical study of 48 weeks duration. In this study, a total of 225 patients with type 2 diabetes mellitus received dapagliflozin as add-on therapy to sitagliptin

(with or without metformin), and 226 received placebo plus sitagliptin (with or without metformin). No additional adverse reactions were identified for the combined use of dapagliflozin and sitagliptin compared with those reported for the individual components (see Table 1).

The safety profile of dapagliflozin in type 2 diabetes mellitus has been evaluated in clinical studies including more than 15000 subjects treated with dapagliflozin. The incidence of adverse reactions was determined using a pre-specified pool of patients from 13 short term (mean duration 22 weeks), placebo-controlled studies in type 2 diabetes. Across these 13 studies, 2360 patients were treated once daily with dapagliflozin 10 mg and 2295 were treated with placebo (either as monotherapy or in combination with other antidiabetic therapies, including add-on therapy to sitagliptin).

In the dedicated cardiovascular (CV) outcomes study with dapagliflozin in patients with type 2 diabetes mellitus (DECLARE), 8574 patients received dapagliflozin 10 mg and 8569 received placebo for a median exposure time of 48 months. In total, there were 30623 patient-years of exposure to dapagliflozin.

Adverse drug reactions

The adverse drug reactions in patients treated with dapagliflozin 10 mg (with or without other anti-diabetic medications, including add-on therapy to sitagliptin) and sitagliptin (as monotherapy) in clinical trials are shown in Table 1. Adverse drug reactions are organised by MedDRA System Organ Class (SOC). Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000) and not known (cannot be estimated from available data).

Table 1 Adverse Drug Reactions Identified from Clinical Trials, by Frequency and System Organ Class (SOC)

System Organ class	Common	Uncommon	Rare
Infections and infestations	Genital infection [1,a,b,c] Urinary tract infection[1,a,c,d] Upper respiratory tract infection[2,e] Nasopharyngitis[2,e]		
Blood and lymphatic system disorders			Thrombocytopenia[2]
Metabolism and nutrition disorders	Hypoglycaemia[2,c]		Diabetic ketoacidosis[1,c,g]
Nervous system disorders	Headache[2]	Dizziness[2]	
Gastrointestinal disorders		Constipation[2]	
Musculoskeletal and connective tissue disorders	Back pain[1,a]		
Renal urinary disorders	polyuria[1,a,f]		

[1] Adverse reaction with dapagliflozin.

[2] Adverse reaction with sitagliptin.

[a] Identified from 13 placebo-controlled studies with dapagliflozin 10 mg in type 2 diabetes mellitus, including 3 monotherapy, 1 initial combination with metformin, 2 add-on to metformin, 2 add-on to insulin, 1 add-on to pioglitazone, 1 add-on to sitagliptin, 1 add-on to glimepiride, and 2 studies with combination add-on therapy.

[b] Genital infection includes the preferred terms, listed in order of frequency reported: vulvovaginal mycotic infections, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection male, penile infection, vulvitis, vaginitis bacterial, and vulval abscess.

[c] See subsection 'Description of selected adverse reactions' below for additional information.

[d] Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

[e] Reported regardless of causal relationship to medication and occurring in at least 5% and more commonly in patients treated with sitagliptin.

[f] Polyuria includes the preferred terms, listed in order of frequency reported: pollakiuria, polyuria, urine output increased.

[g] Identified in a large cardiovascular outcomes study with dapagliflozin in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate.

Description of selected adverse reactions

Genital infections

Dapagliflozin

In the dapagliflozin added-on to sitagliptin (with or without metformin) study, events of genital infections were reported in 9.3% of the patients in the dapagliflozin group and 0.4% in the placebo group. In both groups, the events were mild or moderate in intensity and more common in female than male patients.

In the pooled analysis of 13 short-term, placebo-controlled studies, events of genital infections were reported in 5.5% and 0.6% of patients who received dapagliflozin 10 mg and placebo, respectively. The events of genital infections reported in patients treated with dapagliflozin 10 mg were all mild to moderate. Most events of genital infection responded to an initial course of standard treatment and rarely resulted in discontinuation from the study (0.2% dapagliflozin 10 mg *versus* 0% in placebo). Subjects with a history of recurrent genital infection were more likely to experience an infection. Infections were reported more frequently in females (8.4% dapagliflozin 10 mg *versus* 1.2% placebo) than in males (3.4% dapagliflozin 10 mg *versus* 0.2% placebo). The most frequently reported genital infections were vulvovaginal mycotic infections in females and balanitis in males.

In 9 of the 13 studies in the placebo-controlled pool, long-term data was available. In this short-term plus long-term placebo-pooled analysis (mean duration of treatment was 439.5 days for dapagliflozin 10 mg and 419.0 days for placebo); the proportions of patients with events of genital infections were 7.7% (156/2026) in the dapagliflozin 10 mg group and 1.0% (19/1956) in the placebo group. Of the patients treated with dapagliflozin 10 mg who experienced an infection, 67.9% had only one and 10.9% had 3 or more. Of the patients treated with placebo who experienced an infection, 89.5% had only one and none had 3 or more.

In the DECLARE study, the number of patients with serious adverse events (SAE) of genital infections were few and balanced: 2 (<0.1%) patients in each of the dapagliflozin and placebo groups. There were 74 and 7 patients with non-serious adverse events of genital infections leading to study drug discontinuation in the dapagliflozin group and placebo group, respectively.

In the DAPA-HF study, no patient reported a SAE of genital infections in the dapagliflozin group and one in the placebo group. There were 7 (0.3%) patients with adverse events leading to discontinuations (DAE) due to genital infections in the dapagliflozin group and none in the placebo group. In the DELIVER study, one (<0.1%) patient in each treatment group reported a SAE of genital infections. There were 3 (0.1%) patients with DAEs due to genital infection in the dapagliflozin group and none in the placebo group.

In the DAPA-CKD study, there were 3 (0.1%) patients with SAE of genital infections in the dapagliflozin group and none in the placebo group. There were 3 (0.1%) patients with DAEs due to genital infections in the dapagliflozin group and none in the placebo group.

Cases of phimosis/acquired phimosis have been reported with dapagliflozin concurrent with genital infections and in some cases, circumcision was required.

Urinary tract infections

Dapagliflozin

In the dapagliflozin added-on to sitagliptin (with or without metformin) study, events of urinary tract infections (UTI) were reported in 5.8% of the patients in the dapagliflozin group and 3.5% in the placebo group, and more commonly in females.

In the pooled analysis of 13 short-term, placebo-controlled studies, events of UTI were reported in 4.7% and 3.5% of patients who received dapagliflozin 10 mg and placebo, respectively Most events of urinary tract infections reported in patients treated with dapagliflozin 10 mg were mild to moderate. Most patients responded to an initial course of standard treatment, and urinary tract infections rarely caused discontinuation from the study (0.2% dapagliflozin 10 mg *versus* 0.1% placebo). Subjects with a history of recurrent urinary tract infection were more likely to experience an infection. Infections were more frequently reported in females (8.5% dapagliflozin 10 mg *versus* 6.7% placebo) than in males (1.8% dapagliflozin 10 mg *versus* 1.3% placebo) (See section 4.4 Special warnings and precautions for use).

In the short-term plus long-term placebo-pooled analysis of 9 short-term studies with long term data available the proportions of patients with events of urinary tract infections were 8.6% in the dapagliflozin 10 mg group and 6.2% in the placebo group. Of the patients treated with dapagliflozin 10 mg who experienced an infection, 77.6% had only one and 6.3% had 3 or more. Of the patients treated with placebo who experienced an infection, 77.7% had only one and 9.9% had 3 or more.

In the DECLARE study, there were fewer patients with SAEs of UTI in the dapagliflozin group compared with the placebo group: 79 (0.9%) and 109 (1.3%), respectively.

The number of patients with SAEs of UTI were low and balanced in the DAPA-HF and DELIVER studies: in DAPA-HF there were 14 (0.6%) patients in the dapagliflozin group and 17 (0.7%) in the placebo group and in DELIVER there were 41 (1.3%) patients in the dapagliflozin group and 37 (1.2%) in the placebo group. In the DAPA-HF study, there were 5 (0.2%) patients with DAEs due to UTI in each of the dapagliflozin and placebo groups. In the DELIVER study, there were 13 (0.4%) patients with DAEs due to UTI in the dapagliflozin group and 9 (0.3%) in the placebo group.

In the DAPA-CKD study, there were 29 (1.3%) patients with SAEs of UTI in the dapagliflozin group and 18 (0.8%) patients in the placebo group. There were 8 (0.4%) patients with DAEs due to UTI in the dapagliflozin group and 3 (0.1%) in the placebo group.

Diabetic ketoacidosis (DKA)

Dapagliflozin

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

Hypoglycaemia

Dapagliflozin

The incidence of hypoglycaemia as seen in the dapagliflozin added-on to sitagliptin (with or without metformin) study and in the DECLARE study is shown in Table 2.

Table 2 Incidence of Major[a] and Minor[b] Hypoglycaemia in Controlled Clinical Studies with Dapagliflozin

	Placebo	Dapagliflozin 10 mg
Add-on of dapagliflozin to sitagliptin (with or without metformin) (48 weeks)	**N=226**	**N=225**
Major [n (%)][c]	0	1 (0.4)
Minor [n (%)][c]	3 (1.3)	5 (2.2)
DECLARE study (48 months median exposure)		
All	**N=8569**	**N=8574**
Major [n (%)]	83 (1.0)	58 (0.7)
Patients treated with insulin	**N=4606**	**N=4177**
Major [n (%)]	64 (1.4)	52 (1.2)
Patients treated with a sulfonylurea	**N=4521**	**N=4118**
Major [n (%)]	23 (0.5)	14 (0.3)

[a] Major episodes of hypoglycaemia were defined as symptomatic episodes requiring external (third party) assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value <3 mmol and prompt recovery after glucose or glucagon administration.

[b] Minor episodes of hypoglycaemia were defined as either a symptomatic episode with a capillary or plasma glucose measurement <3.5 mmol regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement <3.5 mmol that does not qualify as a major episode.

[c] Excluding data after rescue.

Sitagliptin

In a pre specified pooled analysis of two monotherapy studies, an add-on to metformin study, and an 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 Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7332 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 7339 patients treated with 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.

Pancreatitis

Sitagliptin

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 section 4.4 Special warnings and precautions for use, Pancreatitis).

In the TECOS study, the incidence of adjudication-confirmed pancreatitis events was 0.3% in sitagliptin-treated patients and 0.2% in placebo-treated patients.

Volume depletion

Dapagliflozin
In the pooled analysis of 13 short-term, placebo-controlled studies, events suggestive of volume depletion (including reports of dehydration, hypovolemia or hypotension) were reported in 1.1% and 0.7% of patients who received dapagliflozin 10 mg and placebo, respectively. Across the pool of 21 active and placebo-controlled studies, serious events occurred in ≤0.2% of patients and were balanced between dapagliflozin 10 mg and comparator (see section 4.4 Special warnings and precautions for use).

Adverse events of volume depletion were more commonly seen in patients with moderate renal impairment.

In the cardiovascular outcomes study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use. In patients with eGFR <60 mL/min/1.73 m^2 at baseline, there were 19 events of serious adverse events suggestive of volume depletion in 604 patients in the dapagliflozin group and 13 events in 658 patients in the placebo group.

Necrotising fasciitis of the perineum (Fournier's gangrene)

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

Events related to decreased renal function

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

In the 13-study, short-term, placebo-controlled pool, mean serum creatinine levels increased a small amount at Week 1 (mean change from baseline: 0.0036 mmol/L dapagliflozin 10 mg versus 0.0007 mmol/L placebo) and decreased toward baseline by Week 24 (mean change from baseline: 0.019 mg/dL dapagliflozin 10 mg versus 0.008 mg/dL placebo). There were no further changes through Week 102.

In the cardiovascular outcomes study, there were fewer patients with marked laboratory abnormalities of creatinine, creatinine clearance, eGFR, and urine albumin to creatinine ratio (UACR) in the dapagliflozin group compared with the placebo group. Fewer renal events (e.g., decreased renal creatinine clearance, renal impairment, increased blood creatinine, and decreased glomerular filtration rate) were reported in the dapagliflozin group compared with the placebo group: 422 (4.9%) and 526 (6.1%), respectively. There were fewer patients with events reported as acute kidney injury in the dapagliflozin group compared with the placebo group: 125 (1.5%) and 175 (2.0%), respectively. There were fewer patients with SAEs of renal events in the dapagliflozin group compared with the placebo group: 80 (0.9%) and 136 (1.6%), respectively. eGFR decreased

over time in both treatment groups. At 1 year, mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.

Post-marketing experience

The adverse drug reactions identified during post-marketing experience with the individual mono-components are shown in Table 3. Because these reactions are reported voluntarily from a population of an uncertain size, it is not always possible to reliably estimate their frequency. Adverse drug reactions are organised by MedDRA System Organ Class (SOC). Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000) and not known (cannot be estimated from available data).

Table 3 Adverse Drug Reactions Identified During Post-marketing Use of Dapagliflozin and Sitagliptin, by Frequency and System Organ Class (SOC)

System Organ Class	Common	Uncommon	Unknown	Very rare
Immune system disorders			Hypersensitivity reactions including anaphylactic responses[2]	
Infections and infestations			Pyelonephritis[1] Urosepsis[1] Necrotising fasciitis of the perineum (Fournier's gangrene) [1] Upper respiratory tract infection[2] Nasopharyngitis[2]	
Respiratory, thoracic and mediastinal disorders			Interstitial lung disease[2]	
Metabolism and nutrition disorders			Ketoacidosis[1]	
Nervous system disorders			Headache[2]	
Gastrointestinal disorders			Vomiting[2] Constipation[2] Acute pancreatitis[2,a] Fatal and non-fatal haemorrhagic and necrotizing pancreatitis[2]	
Skin and subcutaneous tissue disorders		Pruritus[2]	Rash[1,2,b] Angioedema[1,2] Urticaria[2] Cutaneous vasculitis[2] Exfoliative skin conditions including Stevens-Johnson syndrome[2] Bullous pemphigoid[2]	

System Organ Class	Common	Uncommon	Unknown	Very rare
Musculoskeletal and connective tissue disorders			Arthralgia[2] Myalgia[2] Pain in extremity[2] Back pain[2] Arthropathy[2]	
Renal and urinary disorders			Impaired renal function[2] Acute renal failure[2]	Tubulointerstitial nephritis
Investigations	Increased haematocrit			

[1] Adverse reaction with dapagliflozin.

[2] Adverse reaction with sitagliptin.

[a] See subsection 'Description of selected adverse reactions' above for additional information.

[b] Rash includes the following preferred terms, listed in order of frequency in dapagliflozin clinical trials: Rash, Rash generalized, Rash pruritic, Rash macular, Rash maculo-papular, Rash pustular, Rash vesicular, Rash erythematous. In active- and placebo-controlled clinical trials (dapagliflozin, N=5936, all control, N=3403), the frequency of Rash was similar for dapagliflozin (1.4%) and all control (1.4%), respectively, corresponding to the frequency 'common'. There have been postmarketing reports of acute kidney injury, some requiring hospitalisation and dialysis, in patients receiving SGLT2 inhibitors, including dapagliflozin; some reports involved patients younger than 65 years of age.

Reporting suspected adverse effects

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

4.9 OVERDOSE

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

Dapagliflozin/sitagliptin combination

There is no information available on overdose with SIDAPVIA. Experience with the individual mono-components are described below.

Dapagliflozin

Orally administered dapagliflozin has been shown to be safe and well tolerated in healthy subjects at single doses up to 500 mg (50 times the MRHD). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose) with no reports of dehydration, hypotension, or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia for patients treated with dapagliflozin was similar to placebo.

In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) of dapagliflozin were administered for 2 weeks in healthy subjects and type 2 diabetes patients, the incidence of hypoglycaemia for subjects administered dapagliflozin was slightly higher than placebo and was not dose related. Rates of adverse events including dehydration or hypotension for patients treated with dapagliflozin were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters including serum electrolytes and biomarkers of renal function.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by haemodialysis has not been studied.

Sitagliptin

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase 1 multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

Sitagliptin is modestly dialysable. 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 dialysable by peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Dapagliflozin/sitagliptin combination

SIDAPVIA combines the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin and the dipeptidyl peptidase 4 (DPP4) inhibitor sitagliptin with distinct and complementary mechanisms of action to improve glycaemic control.

Dapagliflozin

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

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and preserve renal function. Other effects include an increase in haematocrit and reduction in body weight.

The cardio-renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect. In addition to the osmotic diuretic and related hemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis, adipokines and uric acid may be mechanisms underlying the cardio-renal beneficial effects of dapagliflozin.

Dapagliflozin improves both fasting and postprandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose and/or low GFR, dapagliflozin has a low propensity to cause hypoglycaemia, as the amount of filtrated glucose is small and can be reabsorbed by SGLT1 and unblocked SGLT2 transporters. Dapagliflozin does not impair normal endogenous glucose production in response to

hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta-cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.

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

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

Sitagliptin

Sitagliptin is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP4) 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 physiologic 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 DPP4 inhibitors in animal models of type 2 diabetes mellitus 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 release 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 DPP4 enzyme, which rapidly hydrolyses the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP4, 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 mellitus with hyperglycaemia, these changes in insulin and glucagon levels lead to lower HbA1c and lower fasting and postprandial glucose concentrations. Sitagliptin inhibits DPP4 with nanomolar potency (IC_{50} 18 nM). It does not inhibit the closely-related enzymes DPP8 or DPP9 at therapeutic concentrations. Inhibition of DPP8 or DPP9 is associated with toxicity in preclinical animal models and alteration of immune function *in vitro*.

Clinical trials

Treatment with dapagliflozin added-on to sitagliptin (with or without metformin), in type 2 diabetes mellitus patients, produced clinically relevant and statistically significant improvements in mean change from baseline at Week 24 in HbA1c and fasting plasma glucose (FPG) compared to control (placebo added on to sitagliptin (with or without metformin)). Additionally, a clinically relevant and statistically significant reduction in mean change from baseline in body weight was seen at Week 24.

Glycaemic control

Add-on of dapagliflozin to sitagliptin alone or in combination with metformin

A total of 452 patients with type 2 diabetes mellitus who were drug naive, or who were treated at entry with metformin or a DPP4 inhibitor alone or in combination, and had inadequate glycaemic control (HbA1c ≥7.0% and ≤10.0% at randomization), participated in a 24-week, placebo-controlled study with a 24-week extension period to evaluate dapagliflozin in combination with sitagliptin with or without metformin.

Eligible patients were stratified based on the presence or absence of background metformin (≥1500 mg/day) and within each stratum were randomized to either dapagliflozin 10 mg plus sitagliptin 100 mg once daily or placebo plus sitagliptin 100 mg once daily. Endpoints were tested for dapagliflozin 10 mg *versus* placebo for the total study group (sitagliptin with or without metformin) and for each stratum (sitagliptin alone or sitagliptin with metformin). Thirty-seven percent (37%) of patients were drug naive, 32% were on metformin alone, 13% were on a DPP4 inhibitor alone, and 18% were on a DPP4 inhibitor plus metformin. Dose titration of dapagliflozin, sitagliptin or metformin was not permitted during the study.

The mean age of the total study population was 54.9 years (18% ≥65 years of age), mean body mass index (BMI) was 32.40 kg/m^2 and 54.8% were male. The mean duration of type 2 diabetes mellitus was 5.67 years and the mean baseline HbA1c was 7.93% (HbA1c was slightly lower in patients using metformin [7.83%] than in patients not using metformin [8.03%]).

In combination with sitagliptin (with or without metformin), dapagliflozin 10 mg provided significant improvements in HbA1c, HbA1c in patients with baseline HbA1c ≥8%, and FPG, and significant reduction in body weight compared with the placebo plus sitagliptin (with or without metformin) group at Week 24. These improvements were also seen in the stratum of patients who received dapagliflozin 10 mg plus sitagliptin alone (n=110) compared with placebo plus sitagliptin alone (n=111), and in the stratum of patients who received dapagliflozin 10 mg plus sitagliptin with metformin (n=113) compared with placebo plus sitagliptin with metformin (n=113). Results on primary and key secondary endpoints are displayed in Table 4.

The proportion of patients achieving HbA1c <7% was higher in the dapagliflozin plus sitagliptin (with or without metformin) group (28.3%) compared to the placebo plus sitagliptin (with or without metformin) group (19.4%) at Week 24, using last observation carried forward (LOCF) analysis excluding data after rescue. Nominal $p<0.05$, for the difference between treatment groups.

The adjusted mean change from baseline in seated SBP in the full study population was -1.8 mmHg in the dapagliflozin plus sitagliptin (with or without metformin) group and 0.8 mmHg in the placebo plus sitagliptin (with or without metformin) group at Week 24, using last observation carried forward (LOCF) analysis including data after rescue. Nominal $p<0.05$, for the difference between treatment groups.

The proportion of patients at Week 24 and Week 48 who were rescued or discontinued for lack of glycaemic control (adjusted for baseline HbA1c) was higher for sitagliptin with or without metformin (40.5% and 56.5%, respectively) than for dapagliflozin plus sitagliptin with or without metformin (19.5% and 32.6%, respectively).

Table 4 Results of a 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Sitagliptin with or without Metformin

Efficacy Parameter	Sitagliptin 100 mg					
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
	Full study population		without Metformin		with Metformin	
	N=223†	N=224†	N=110†	N=111†	N=113†	N=113†
HbA1c (%)						
Baseline (mean)	7.90	7.97	7.99	8.07	7.80	7.87
Change from baseline (adjusted mean‡)	−0.45	0.04	−0.47	0.10	−0.43	−0.02
Difference from placebo (adjusted mean‡) (95% CI)	−0.48§ (−0.62, −0.34)		−0.56§ (−0.79, −0.34)		−0.40§ (−0.58, −0.23)	
HbA1c in patients with baseline HbA1c ≥8% (%)						
Baseline (mean)	8.65 (N=94)	8.68 (N=99)	8.62	8.70	8.68	8.65
Change from baseline (adjusted mean‡)	−0.80	0.03	−0.81	0.06	−0.79	0.0
Difference from placebo (adjusted mean‡) (95% CI)	-0.83§ (-1.05, -0.62)		-0.87§ (-1.18, -0.55)		-0.80§ (-1.10, -0.49)	
FPG (mmol/L)						
Baseline (mean)	9.0	9.1	8.7	9.0	9.2	9.2
Change from baseline (adjusted mean‡)	−1.3	0.2	−1.2	0.3	−1.5	0.2
Difference from placebo (adjusted mean‡) (95% CI)	−1.6 § (−1.9, −1.2)		−1.5§ (−2.0, −0.9)		−1.6§ (−2.1, −1.1)	
Body Weight (kg)						
Baseline (mean)	91.02	89.23	88.01	84.20	93.95	94.17
Change from baseline (adjusted mean‡)	−2.14	−0.26	−1.91	−0.06	−2.35	−0.47
Difference from placebo (adjusted mean‡) (95% CI)	−1.89§ (−2.37, −1.40)		−1.85§ (−2.47, −1.23)		−1.87§ (−2.61, −1.13)	
Seated SBP at Week 8 in patients with baseline seated SBP ≥130 mmHg (mmHg)						

Efficacy Parameter	Sitagliptin 100 mg					
	Dapagliflozin 10 mg	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**
	Full study population		**without Metformin**		**with Metformin**	
Baseline (mean)	140.5 (N=101)	139.3 (N=111)	138.5	137.9	141.9	140.3
Change from baseline (adjusted mean‡)	−6.0	−5.1	−6.6	−4.2	−5.3	−5.5
Difference from placebo (adjusted mean‡) (95% CI)	−0.86 (−3.8, 2.0)		−2.4 (−6.4, 1.7)		0.2 (–3.85, 4.32)	
2-hour PPG¶ (mmol/L)						
Baseline (mean)	12.7	12.6	12.5	12.8	12.8	12.3
Change from baseline (adjusted mean‡)	−2.7	−0.3	−2.6	−0.1	−2.7	−0.4
Difference from placebo (adjusted mean‡) (95% CI)	−2.4 (−2.9, −1.9)		−2.4 (−3.1, −1.8)		−2.3 (−1.8, −1.5)	
Patients with HbA1c decrease ≥ 0.7% (adjusted %)	35.3	16.6	42.8	17.2	28.0	16.0
Difference from placebo (adjusted %) (95% CI)	18.7 (11.1, 26.4)		25.6 (14.3, 36.8)		12.1 (1.7, 22.5)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 *versus* placebo.

¶ 2-hour PPG level as a response to a 75-gram oral glucose tolerance test (OGTT).

Glycaemic control in special populations

Use in patients with type 2 diabetes mellitus and hypertension

Dapagliflozin

In the pre-specified pooled analysis of 13 placebo-controlled studies (see section 4.8 Adverse effects (Undesirable effects)), treatment with dapagliflozin 10 mg resulted in a systolic blood pressure change from baseline of –3.7 mmHg and diastolic blood pressure of –1.8 mmHg versus –0.5 mmHg systolic and -0.5 mmHg diastolic blood pressure for the placebo group at Week 24. Similar reductions were observed up to 104 weeks.

In two 12-week, placebo-controlled studies a total of 1,062 patients with inadequately controlled type 2 diabetes and hypertension (despite pre-existing stable treatment with an ACE-I or ARB in one study and an ACE-I or ARB plus one additional antihypertensive treatment in another study) were treated with dapagliflozin 10 mg or placebo. At Week 12 for both studies, dapagliflozin 10 mg plus usual antidiabetic treatment provided improvement in HbA1c, and decreased the placebo-corrected systolic blood pressure on average by 3.1 and 4.3 mmHg, respectively.

Use in patients with type 2 diabetes mellitus and renal impairment

Dapagliflozin

The glycaemic efficacy and safety of dapagliflozin was evaluated in a dedicated study of patients with eGFR ≥45 to <60 mL/min/1.73 m^2.

In this randomized, double blind, placebo-controlled trial a total of 321 adult patients with type 2 diabetes mellitus and eGFR ≥45 to <60 mL/min/1.73 m^2 (moderate renal impairment subgroup Chronic Kidney Disease [CKD] 3A), with inadequate glycaemic control on current treatment regimen, were treated with dapagliflozin 10 mg or placebo. At Week 24, dapagliflozin 10 mg (n=159) provided significant improvements in HbA1c, FPG, body weight and SBP compared with placebo (n=161) (Table 5). The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change was −0.37% and −0.34%, respectively. The mean change from baseline in FPG and the placebo-corrected mean FPG was -1.19mmol/L and -0.92 mmol/L, respectively. The mean body weight reduction (percentage) and the placebo-corrected mean body weight reduction was -3.42% and -1.43%, respectively. The mean reduction in seated SBP and the placebo-corrected mean reduction in seated SBP was -4.8 mmHg and -3.1 mmHg, respectively.

Table 5 Results at Week 24 in a Placebo-Controlled Study of Dapagliflozin Treatment in Diabetic Patients with Moderate Renal Impairment (Class 3A, eGFR ≥45 to <60 mL/min/1.73 m^2)

Efficacy Parameter	**Dapagliflozin 10 mg N=159**	**Placebo N=161**
HbA1c (%)		
Baseline (mean)	8.35	8.03
Change from baseline (adjusted mean*)	-0.37	-0.03
Difference from placebo (adjusted mean*) (95% CI)	-0.34§ (-0.53, -0.15)	
FPG (mmol/L)		
Baseline (mean)	10.16	9.62
Change from baseline (adjusted mean*)	-1.19	-0.27
Difference from placebo (adjusted mean*) (95% CI)	-0.92§ (-1.48, -0.36)	
Body Weight (percentage)		
Baseline (mean)	92.51	88.30
% Change from baseline (adjusted mean*)	-3.42	-2.02
Difference from placebo (adjusted mean*) (95% CI)	-1.43§ (-2.15, -0.69)	
Seated Systolic Blood Pressure (mmHg)		
Baseline (mean)	135.7	135.0
Change from baseline (adjusted mean*)	-4.8	-1.7
Difference from placebo (adjusted mean*) (95% CI)	-3.1¶ (-6.3, 0.0)	

* Least squares mean adjusted for baseline value.

§ p-value ≤0.001.

¶ p-value <0.05.

The safety profile of dapagliflozin in the study was consistent with that in the general population of patients with type 2 diabetes mellitus. Mean eGFR decreased initially during the treatment period in

the dapagliflozin group and subsequently remained stable during the 24-week treatment period (dapagliflozin: -3.39 mL/min/1.73 m^2 and placebo: -0.90 mL/min/1.73 m^2). At 3 weeks after termination of dapagliflozin, the mean change from baseline in eGFR in the dapagliflozin group was similar to the mean change in the placebo group (dapagliflozin: 0.57 mL/min/1.73 m^2 and placebo: -0.04 mL/min/1.73 m^2).

The efficacy and safety of dapagliflozin was also assessed in a study of 252 patients with diabetes with eGFR ≥30 to <60 mL/min/1.73 m^2 (moderate renal impairment subgroup CKD 3A, eGFR ≥45 to <60 mL/minute/1.73 m^2 and CKD 3B, eGFR ≥30 to <45 mL/minute/1.73 m^2). Dapagliflozin treatment did not show a significant placebo corrected change in HbA1c in the overall study population (CKD 3A and CKD 3B combined) at 24 weeks. At Week 52, dapagliflozin was associated with a greater reduction in mean eGFR (dapagliflozin 10 mg −4.46 mL/min/1.73 m^2 and placebo −2.58 mL/min/1.73 m^2). At Week 104, these changes persisted (eGFR: dapagliflozin 10 mg −3.50 mL/min/1.73 m^2 and placebo −2.38 mL/min/1.73 m^2). With dapagliflozin 10 mg, eGFR reduction evident at Week 1 and remained stable through Week 104, while placebo-treated patients had a slow continuous decline through Week 52 that stabilised through Week 104.

At Week 52 and persisting through Week 104, greater increases in mean parathyroid hormone (PTH) and serum phosphorus were observed in this study with dapagliflozin 10 mg compared to placebo, where baseline values of these analytes were higher. Elevations of potassium of ≥6 mEq/L were more common in patients treated with placebo (12.0%) than those treated with dapagliflozin 10 mg (4.8%) during the cumulative 104-week treatment period. The proportion of patients discontinued for elevated potassium, adjusted for baseline potassium, was higher for the placebo group (14.3%) than for the dapagliflozin 10 mg group (6.7%).

Overall, there were 13 patients with an adverse event of bone fracture reported in the dapagliflozin group. Eight (8) of these 13 fractures were in patients who had eGFR 30 to 45 mL/min/1.73 m^2 and 10 of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the site of fracture. No bone fractures were reported in the dedicated study of patients with eGFR ≥45 to <60 mL/min/1.73 m^2 (CKD 3A). No fractures were reported in the placebo group.

Supportive study

Dapagliflozin dual energy X-ray absorptiometry in type 2 diabetic patients

Due to the mechanism of action of dapagliflozin, a study was done to evaluate body composition and bone mineral density in 182 patients with type 2 diabetes mellitus. Treatment with dapagliflozin 10 mg added on to metformin over a 24-week period provided significant improvements compared with placebo plus metformin, respectively, in body weight (mean change from baseline: −2.96 kg *versus* −0.88 kg); waist circumference (mean change from baseline: −2.51 cm *versus* −0.99 cm), and body-fat mass as measured by DXA (mean change from baseline: −2.22 kg *versus* −0.74 kg) rather than lean tissue or fluid loss. Dapagliflozin plus metformin treatment showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (change from baseline: −322.6 cm^3 *versus* −8.7 cm^3) in an MRI substudy. In an ongoing extension of this study to week 50, there was no important change in bone mineral density for the lumbar spine, femoral neck or total hip seen in either treatment group (mean change from baseline for all anatomical regions <0.5%, 7/89 dapagliflozin and 4/91 comparator subjects showed a decrease of 5% or more). These effects were sustained in a further extension of the study to 102 weeks where no important changes in BMD for the lumbar spine, femoral neck or total hip in either treatment group were observed.

Cardiovascular outcomes studies in patients with type 2 diabetes mellitus

Dapagliflozin

Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicentre, randomized, double-blind, placebo-controlled clinical study conducted to determine the effect of dapagliflozin compared with placebo on cardiovascular (CV) and renal outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either at least two additional CV risk factors (age ≥55 years in men or ≥60 years in women and one or more of dyslipidaemia, hypertension or current tobacco use) without having had a CV event at baseline (primary prevention) or established CV disease (secondary prevention).

Of 17160 randomized patients, 6974 (40.6%) had established CV disease and 10186 (59.4%) did not have established CV disease. 8582 patients were randomized to dapagliflozin 10 mg and 8578 to placebo and were followed for a median of 4.2 years.

The mean age of the study population was 63.9 years, 37.4% were female, 79.6% were White, 3.5% Black or African-American and 13.4% Asian. In total, 22.4% had had diabetes for ≤5 years, mean duration of diabetes was 11.9 years. Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m^2.

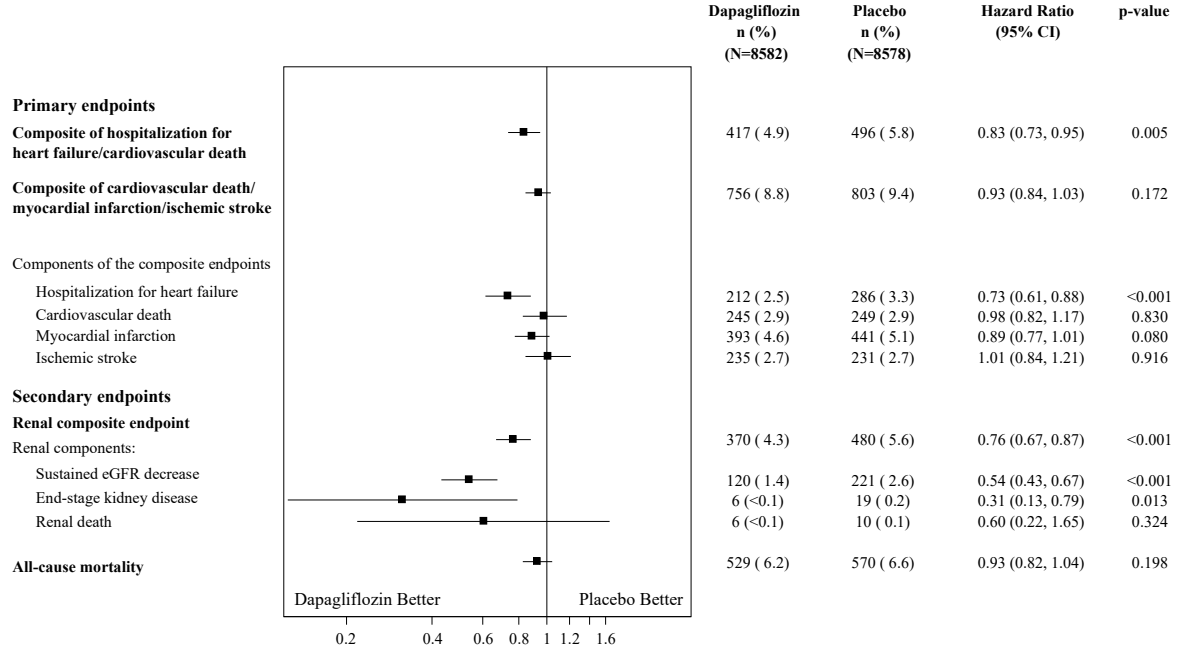
At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 mL/min/1.73 m^2, 7.4% of patients had eGFR <60 mL/min/1.73 m^2 and 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ration [UACR] ≥30 to ≤300 mg/g or >300 mg/g, respectively).

Most patients (98.1%) used one or more diabetic medications at baseline, 82.0% of the patients were being treated with metformin, 40.9% with insulin, 42.7% with a sulfonylurea, 16.8% with a DPP4 inhibitor, and 4.4% with a GLP-1 agonist.

Approximately 81.3% of patients were treated with ACEi or ARB, 75.0% with statins, 61.1% with antiplatelet therapy, 55.5% with acetylsalicylic acid, 52.6% with beta-blockers, 34.9% with calcium channel blockers, 22.0% with thiazide diuretics and 10.5% with loop diuretics.

Results on primary and secondary endpoints are displayed in Figure 1.

Figure 1 Treatment effects for the primary composite endpoints and their components, and the secondary endpoints and components



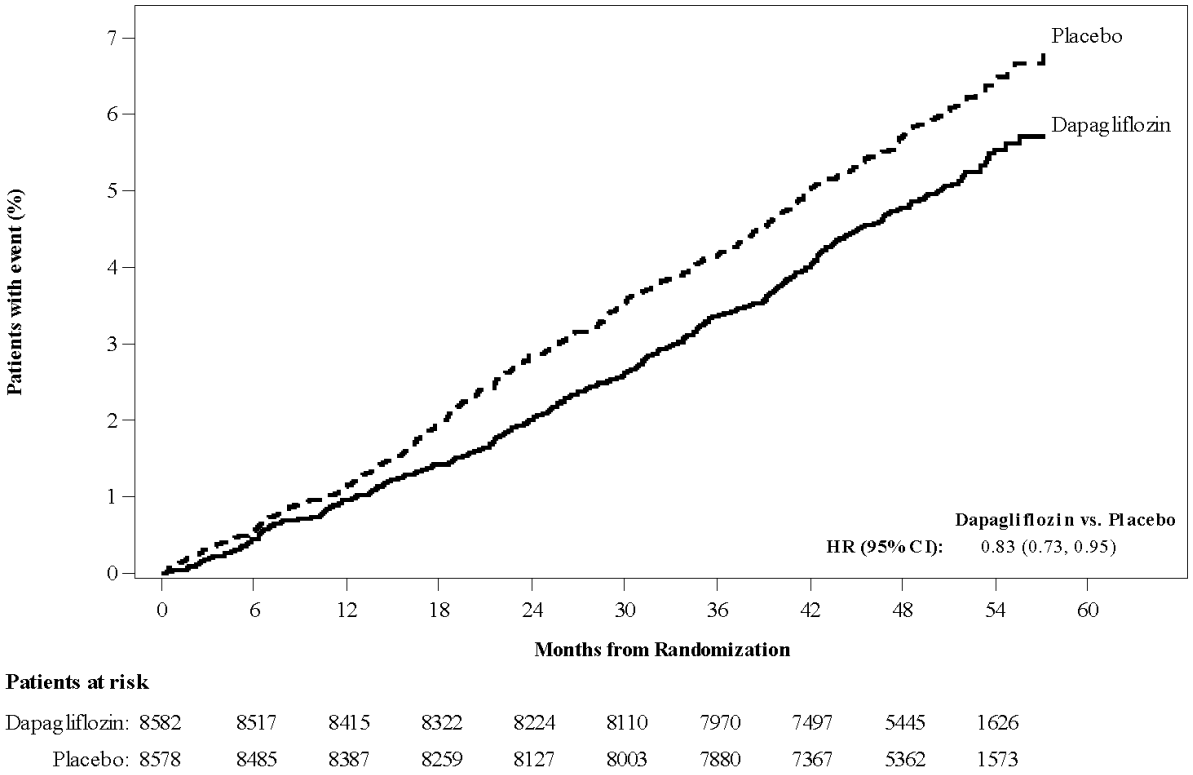
p-values are two-sided p-values for primary endpoints and nominal p-values for secondary endpoints and single components. Time to first event was analysed in a Cox proportional hazards model. The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.
Renal composite endpoint is defined as sustained confirmed ≥40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or ESKD (dialysis ≥90 days or kidney transplantation, sustained confirmed eGFR <15 mL/min/1.73 m^2) and/or renal or CV death.
CI=confidence interval.

Hospitalisation for heart failure or cardiovascular death

Dapagliflozin 10 mg was superior to placebo in preventing the primary composite endpoint of hospitalization for heart failure or CV death (Hazard Ratio [HR] 0.83 [95% CI 0.73, 0.95]; p=0.005) (Figure 2).

Exploratory analyses of the single components suggest that the difference in treatment effect was driven by hospitalization for heart failure (HR 0.73 [95% CI 0.61, 0.88]) (Figure 1), with no clear difference in CV death (HR 0.98 [95% CI 0.82 to 1.17]).

Figure 2 Time to first occurrence of hospitalization for heart failure or cardiovascular death



Patients at risk

Dapagliflozin:	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
Placebo:	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

Patients at risk is the number of patients at risk at the beginning of the period.
CI Confidence interval, HR Hazard ratio.

Major adverse cardiovascular events

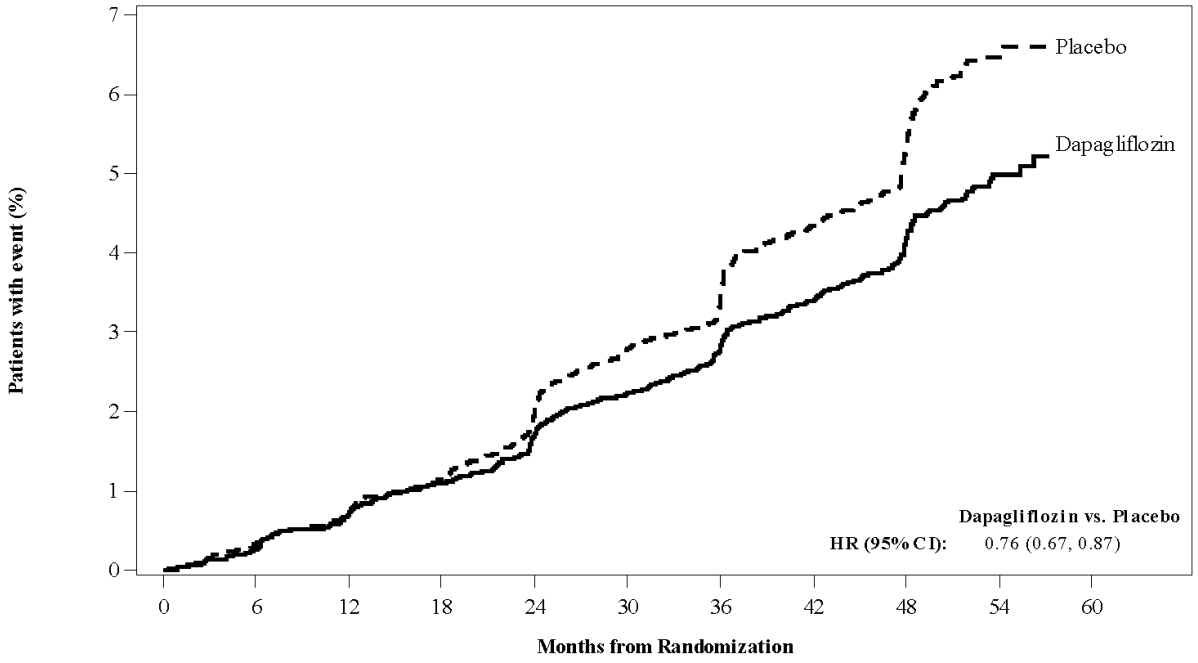
Dapagliflozin demonstrated cardiovascular safety (tested as non-inferiority versus placebo for the composite of CV death, myocardial infarction or ischemic stroke [MACE]; one-sided p<0.001).

Nephropathy

The composite of confirmed sustained eGFR decrease, ESKD, renal or CV death was a secondary variable in the DECLARE study. Because confirmatory testing stopped before the secondary variables were assessed, the analyses of the secondary variables should be considered exploratory.

Dapagliflozin reduced the incidence of events of the composite of confirmed sustained eGFR decrease, ESKD, renal or CV death (HR 0.76 [95% CI 0.67, 0.87]; nominal p<0.001, Figure 3). The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, ESKD and renal death (Figure 1), and was observed both in patients with and without CV disease.

Figure 3 Time to first occurrence of sustained eGFR decrease, ESKD, renal or CV death



Patients at risk

Dapagliflozin:	8582	8533	8436	8347	8248	8136	8009	7534	5472	1637
Placebo:	8578	8508	8422	8326	8200	8056	7932	7409	5389	1589

Patients at risk is the number of patients at risk at the beginning of the period.

Renal composite endpoint defined as sustained confirmed eGFR decrease ≥40% to eGFR <60 mL/min/1.73 m^2 and/or ESKD and/or renal or CV death.

CI Confidence interval; HR Hazard ratio.

When evaluating the renal components, there were 127 and 238 events of new or worsening nephropathy (sustained eGFR decrease, ESKD or renal death) in patients in the dapagliflozin and placebo groups, respectively. The HR for time to nephropathy was 0.53 (95% CI 0.43, 0.66) for dapagliflozin versus placebo.

Beneficial effects of dapagliflozin on renal outcomes were also observed for albuminuria, e.g.,

- In patients without pre-existing albuminuria, dapagliflozin reduced the incidence of sustained albuminuria (UACR >30 mg/g) compared with placebo (HR 0.79 [95% CI 0.72, 0.87].
- In patients without pre-existing macroalbuminuria, new onset of macroalbuminuria (UACR >300 mg/g) was reduced in the dapagliflozin group compared with the placebo group (HR 0.54 [95% CI 0.45, 0.65].
- In patients with pre-existing macroalbuminuria, regression of macroalbuminuria was greater in the dapagliflozin group compared with the placebo group (HR 1.82 [95% CI 1.51, 2.20].

The treatment benefit of dapagliflozin over placebo was observed both in patients with and without existing renal impairment.

Sitagliptin

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a randomised study in 14671 patients in the intention-to-treat population with an HbA1c of ≥6.5 to 8.0% with established CV disease who received sitagliptin (7332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥30 and <50 mL/min/1.73 m^2) or placebo (7339) 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 2004 patients ≥75 years of age and 3324 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 sitagliptin 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, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal 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, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalisation for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes mellitus (Table 6).

Table 6 Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	Sitagliptin 100 mg		**Placebo**			
	N (%)	**Incidence rate per 100 patient-years***	**N (%)**	**Incidence rate per 100 patient-years***	**Hazard Ratio (95% CI)**	**p-value†**
Analysis in the Intention-to-Treat Population						
Number of patients	**7332**		**7339**			
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

	Sitagliptin 100 mg		Placebo			
	N (%)	Incidence rate per 100 patient-years*	N (%)	Incidence rate per 100 patient-years*	Hazard Ratio (95% CI)	p-value†
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.

Clinical safety

Events related to decreased renal function - dapagliflozin

In the 13-study, short-term, placebo-controlled pool, mean serum creatinine levels increased a small amount at Week 1 (mean change from baseline: 0.041 mg/dL dapagliflozin 10 mg *versus* 0.008 mg/dL placebo) and decreased toward baseline by Week 24 (mean change from baseline: 0.019 mg/dL dapagliflozin 10 mg *versus* 0.008 mg/dL placebo). There were no further changes through Week 102.

In the DECLARE study, there were fewer patients with marked laboratory abnormalities of creatinine, creatinine clearance, eGFR, and UACR in the dapagliflozin group compared with the placebo group. Fewer renal events (e.g., decreased renal creatinine clearance, renal impairment, increased blood creatinine, and decreased glomerular filtration rate) were reported in the dapagliflozin group compared with the placebo group: 422 (4.9%) and 526 (6.1%), respectively. There were fewer patients with events reported as acute kidney injury in the dapagliflozin group compared with the placebo group: 125 (1.5%) and 175 (2.0%), respectively. There were fewer patients with SAEs of renal events in the dapagliflozin group compared with the placebo group: 80 (0.9%) and 136 (1.6%), respectively.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of the individual mono-components were generally similar in healthy subjects and in patients with type 2 diabetes mellitus.

Dapagliflozin/sitagliptin combination

Bioequivalence has been confirmed between the SIDAPVIA 10 mg/100 mg tablet and the individual dapagliflozin 10 mg and sitagliptin 100 mg tablets after single dose administration in the fasted state in healthy subjects.

Absorption

Dapagliflozin

Dapagliflozin is rapidly and well absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) are usually attained within

2 hours after administration in the fasted state. The C_{max} and AUC values increase proportionally to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Food has relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects. Administration with a high-fat meal decreases dapagliflozin C_{max} by up to 50% and prolonged T_{max} by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Sitagliptin

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.

The absolute bioavailability of sitagliptin is approximately 87%. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, it may be administered with or without food.

Distribution

Dapagliflozin

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

Sitagliptin

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

Metabolism

Dapagliflozin

Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, with a molar plasma AUC 52% higher than that of dapagliflozin itself at the clinical dose, is an inactive metabolite and does not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism is a minor clearance pathway in humans.

Sitagliptin

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 DPP4 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

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin. After administration of 50 mg [^{14}C]-dapagliflozin dose, 96% is recovered; 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects.

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. Sitagliptin accumulates only minimally with multiple doses. The 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-gp, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a P-gp inhibitor, did not reduce the renal clearance of sitagliptin.

Special populations

Renal impairment

Dapagliflozin

At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes mellitus and mild, moderate, or severe renal impairment (as determined by iohexol clearance) had mean systemic exposures of dapagliflozin that were 32%, 60%, and 87% higher, respectively, than those of patients with type 2 diabetes mellitus and normal renal function. At dapagliflozin 20 mg once-daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal-glucose clearance or 24-hour glucose excretion. The renal-glucose clearance and 24-hour glucose excretion were lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function, and 85, 52, 18, and 11 g of glucose/day was excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate, or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of haemodialysis on dapagliflozin exposure is not known.

Sitagliptin

Compared to normal healthy control subjects, plasma AUC of sitagliptin (50 mg) was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment (eGFR ≥60 mL/min/1.73 m^2 to <90 mL/min/1.73 m^2) and patients with moderate renal impairment (GFR ≥45 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2), respectively. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (GFR ≥30 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2), and approximately 4-fold in patients with severe renal impairment (GFR <30 mL/min/1.73 m^2), including in patients with ESKD on haemodialysis. Sitagliptin was modestly removed by haemodialysis (13.5% over a 3- to 4-hour

haemodialysis session starting 4 hours post dose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with GFR <45 mL/min/1.73m^2 (see section 4.4 Special warnings and precautions for use).

Hepatic impairment

Dapagliflozin

A single-dose (10 mg) dapagliflozin clinical pharmacology study was conducted in patients with mild, moderate, or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls in order to compare the pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between patients with hepatic impairment compared to healthy subjects. In patients with mild or moderate hepatic impairment, mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively. SIDAPVIA should not be used in patients with severe hepatic impairment (see section 4.4 special warnings and precautions for use).

Sitagliptin

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. These differences are not considered to be clinically meaningful. No dose adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤9). 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.

Age

Dapagliflozin

No dosage adjustment for dapagliflozin from the dose of 10 mg once daily is recommended on the basis of age.

The effect of age (young: ≥18 to <40 years [n=105] and elderly: ≥65 years [n=224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥40 to <65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10.4% lower than in the reference group (90% CI; 87.9, 92.2%) and 25% higher in elderly patients compared to the reference group (90% CI; 123, 129%). However, an increase exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusion regarding exposure in patients >70 years old.

Sitagliptin

No dose adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase 1 and Phase 2 data. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Paediatric and adolescent patients

Dapagliflozin

Pharmacokinetics in the paediatric and adolescent population have not been studied.

Sitagliptin

The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18% lower compared to historical data from adult patients with type 2 diabetes for a 100 mg dose.

No studies with sitagliptin have been performed in paediatric patients < 10 years of age.

Gender

Dapagliflozin

No dosage adjustment from the dose of 10 mg once daily is recommended for dapagliflozin on the basis of gender. Gender was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. The mean dapagliflozin AUC_{ss} in females (n=619) was estimated to be 22% higher than in males (n=634) (90% CI; 117,124).

Sitagliptin

No dosage adjustment is necessary based on gender of the patient. Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase 1 pharmacokinetic data and on a population pharmacokinetic analysis of Phase 1 and Phase 2 data.

Race

Dapagliflozin

No dosage adjustment from the dapagliflozin dose of 10 mg once daily is recommended on the basis of race. Race (white, black [African descent], or Asian) was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. Differences in systemic exposures between these races were small. Compared to whites (n=1147), Asian subjects (n=47) had no difference in estimated mean dapagliflozin systemic exposures (90% CI range; 3.7% lower, 1% higher). Compared to whites, black (African descent) subjects (n=43) had 4.9% lower estimated mean dapagliflozin systemic exposures (90% CI range; 7.7% lower, 3.7% lower).

Sitagliptin

No dosage adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase 1 pharmacokinetic data and on a population pharmacokinetic analysis of Phase 1 and Phase 2 data including subjects of white, Hispanic, black, Asian, and other racial groups.

Body weight

Dapagliflozin

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

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

Sitagliptin

No dosage adjustment is necessary based on Body Mass Index (BMI). BMI had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase 1 pharmacokinetic data and on a population pharmacokinetic analysis of Phase 1 and Phase 2 data.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Dapagliflozin

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

Sitagliptin

Sitagliptin was not mutagenic or clastogenic in a battery of genetic toxicology studies, including the Ames bacterial mutagenicity assay, a chromosome aberration assay in Chinese hamster ovary 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* mouse micronucleus assay.

Carcinogenicity

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

Dapagliflozin

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

Sitagliptin

A two-year carcinogenicity study was conducted in rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of focal eosinophilic cellular alterations in the liver in both sexes at 150 mg/kg/day and at 500 mg/kg/day. There was an increased incidence of basophilic cellular alterations in females at 500 mg/kg/day. Eosinophilic and basophilic cellular alterations are regarded as preneoplastic lesions. There was an increase in hepatic adenomas and carcinomas in males, and hepatic carcinomas in females at 500 mg/kg/day. Systemic exposure in rats at 150 and 500 mg/kg/day are 19 and 58 times, respectively, that of humans at 100 mg/day. The no-observed effect level for induction of hepatic neoplasia in rats was 150 mg/kg/day, producing exposure approximately 19-fold higher than the human exposure at the 100 mg/day clinical dose. The increased incidence of hepatic tumours 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 human exposure at the clinical dose of 100 mg/day).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Core tablet: croscarmellose sodium, crospovidone, microcrystalline cellulose, mannitol, magnesium stearate, calcium hydrogen phosphate and sodium stearylfumarate.

Film coating: polyvinyl alcohol, titanium dioxide, macrogol 3350, purified talc 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 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

The film coated tablets are packed into aluminium/aluminium blisters in pack sizes of 7 (sample pack) and 28 tablets.

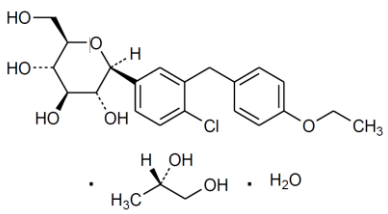
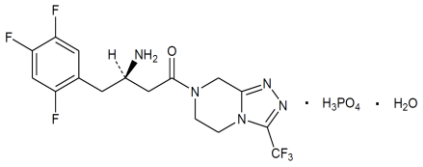
*not all pack sizes may be available in Australia.

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

	Dapagliflozin	**Sitagliptin**
		
Chemical name	(1S)-1,5-Anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-D-glucitol, (S)-propylene glycol, monohydrate	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
Molecular formula	$C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$	$C_{16}H_{15}F_6N_5O \bullet H_3PO_4 \bullet H_2O$
Molecular weight	502.98	523.32

Physicochemical characteristics	Dapagliflozin drug substance is a white to off-white powder, is non-hygroscopic, crystalline. Dapagliflozin is non-ionizable; thus, its aqueous solubility and partition coefficient are not affected by changes in pH. Dapagliflozin is a Biopharmaceutical Classification System (BCS) Class III drug.	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. The pH of a saturated water solution of sitagliptin phosphate monohydrate is 4.4. The partition coefficient is 1.8 and the pKa is 7.7.

CAS number

Dapagliflozin propanediol monohydrate	Sitagliptin phosphate monohydrate
960404-48-2	654671-77-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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

Telephone: 1800 805 342

9 DATE OF FIRST APPROVAL

07 June 2024

10 DATE OF REVISION

1 May 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Changes to warning statement in relation to ketoacidosis and surgery. Addition of increased haematocrit as a warning.
4.8	Inclusion of text in relation to adverse events: increased haematocrit, phimosis and tubulointerstitial nephritis.

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