SIDAPVIA®
(dapagliflozin/sitagliptin)

1. NAME OF THE MEDICINAL PRODUCT

SIDAPVIA 10 mg/ 100 mg film-coated tablets

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 excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Film-coated tablets.

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.

Limitations of use
SIDAPVIA is not indicated for use in patients with type 1 diabetes mellitus.

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

SIDAPVIA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using SIDAPVIA (see Section 4.4 Special warnings and special precautions for use).

4.2 Posology and method of administration

Posology

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 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 Section 5.2 Pharmacokinetic properties). Renal function should be evaluated prior to initiation of SIDAPVIA and periodically thereafter.

Hepatic impairment

SIDAPVIA should not be used in patients with severe hepatic impairment (see Section 5.2 Pharmacokinetic properties).

Paediatric and adolescent patients

Safety and effectiveness of SIDAPVIA in paediatric and adolescent patients have not been established.

Elderly patients

Older patients are more likely to have decreased renal function. The renal function recommendations provided for all patients also apply to elderly patients (see Section 4.4 Special warnings and special precautions for use).

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 special precautions for use and 4.8 Undesirable effects).

4.4 Special warnings and special precautions for use

Use in patients with 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.

Ketoacidosis in patients with diabetes mellitus

There have been reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 1 and type 2 diabetes mellitus taking dapagliflozin and other sodium glucose cotransporter 2 (SGLT2) inhibitors. SIDAPVIA is not indicated for the treatment of patients with type 1 diabetes mellitus.

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, discontinuation or temporary interruption of SIDAPVIA should be considered and the patient should be promptly evaluated.

Treatment should be interrupted in patients who are hospitalized for major surgical procedures or acute serious medical illnesses. Consider monitoring for ketoacidosis and temporarily discontinuing SIDAPVIA in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting SIDAPVIA.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction, reduced caloric intake or increased insulin requirements due to infections, illness, or surgery and alcohol abuse. SIDAPVIA should be used with caution in these patients.

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.

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. 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 Undesirable effects).

Acute pancreatitis

Use of dipeptidyl peptidase 4 (DPP4) inhibitors, including sitagliptin, has been associated with a risk of developing acute pancreatitis. 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 (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, SIDAPVIA should be discontinued; if acute pancreatitis is confirmed, SIDAPVIA should not be restarted. Caution should be exercised in patients with a history of pancreatitis (see Section 4.8 Undesirable effects).

Arthralgia

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

Use in patients at risk for volume depletion

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).

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 anti-hypertensive therapy with a history of hypotension or elderly patients.

For patients receiving SIDAPVIA, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended.

Temporary interruption of SIDAPVIA should be considered for patients who develop volume depletion.

Necrotising Fasciitis of the Perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors (see section 4.8 Undesirable effects). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, SIDAPVIA should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

4.5 Interaction with other medicinal products and other forms of interaction

Dapagliflozin and sitagliptin

In interaction studies conducted in healthy subjects using mainly single dose studies, dapagliflozin did not alter the pharmacokinetics of sitagliptin, and the pharmacokinetics of dapagliflozin was not altered by sitagliptin..

Dapagliflozin

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

In in vitro studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP1A2, 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.

Co-administration of dapagliflozin and bumetanide did not meaningfully change the pharmacodynamic effect of dapagliflozin to increase urinary glucose excretion in healthy subjects.

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.

In interaction studies conducted in healthy subjects, using mainly a single dose design, 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.

Co-administration of dapagliflozin and bumetanide did not meaningfully alter the steady-state pharmacodynamic responses (urinary sodium excretion, urine volume) to bumetanide in healthy subjects.

Dapagliflozin did not affect the anticoagulant activity of warfarin as measured by the prothrombin time (International Normalized Ratio [INR]).

Diuretics: Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Sitagliptin

In Vitro Assessment of Drug Interactions

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

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

In Vivo Assessment of Drug Interactions

Effects of Sitagliptin on Other Drugs

In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing in vivo evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT).

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 Cmax by 18%.

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

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

Simvastatin: Single-dose pharmacokinetics of simvastatin, a CYP3A4 substrate, was 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 was not meaningfully altered in subjects receiving multiple daily doses of sitagliptin, indicating that sitagliptin is not an inhibitor of CYP2C8-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. Because S(-) warfarin is primarily metabolized by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.

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

Effects of Other Drugs on Sitagliptin

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

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.

Cyclosporine: A study was conducted to assess the effect of cyclosporine, 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 cyclosporine increased the AUC and Cmax 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.

Other interactions

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

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

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

4.6 Pregnancy and lactation

Pregnancy

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. When pregnancy is detected, treatment with SIDAPVIA should be discontinued.

Dapagliflozin

In the time period corresponding to the second and third trimesters of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny (see Section 5.3 Preclinical study data).

In conventional studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the first trimester period of nonrenal organogenesis in humans. No developmental toxicities were observed in rabbits at any dose tested (1191× the maximum recommended human dose [MRHD]). In rats, dapagliflozin was neither embryolethal nor teratogenic (1441× the MRHD) in the absence of maternal toxicity.

Sitagliptin

Studies in animals have shown reproductive toxicity at high doses (see Section 5.3 Preclinical study data). The potential risk for humans is unknown.

Lactation

Dapagliflozin/sitagliptin combination

SIDAPVIA should 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 (see Section 5.3 Preclinical study data).

Sitagliptin

Animal studies have shown excretion of sitagliptin in breast milk (see Section 5.3 Preclinical study data).

Fertility

Dapagliflozin/sitagliptin combination

The effect of SIDAPVIA or its mono components on fertility in humans has not been studied.

Dapagliflozin

In male and female rats, dapagliflozin showed no effects on fertility at any dose tested (see Section 5.3 Preclinical study data).

Sitagliptin

Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility (see Section 5.3 Preclinical study data).

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 is anticipated to have no 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 Undesirable effects

Clinical Trials

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 antidiabetic 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 with Dapagliflozin and Sitagliptin from Placebo-Controlled 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	Pollakiuria[1,a] and 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] Multiple adverse events terms, including vulvovaginal infections and candidiasis, balanoposthitis, balanitis candida, penile abscess, penile infection, vulval abscess and vaginitis bacterial.

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

[d] Multiple adverse events terms, including genitourinary tract infection, cystitis, pyelonephritis, trigonitis, urethritis and prostatitis.

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

[f] Represents multiple adverse events terms, including polyuria, urine output increased.

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

Post-marketing experience

The adverse drug reactions identified during post-marketing experience with the individual mono-components are shown in Table 2. 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 2 Adverse Drug Reactions Identified During Post-marketing Use of Dapagliflozin and Sitagliptin, by Frequency and System Organ Class (SOC)

System Organ Class	Uncommon	Unknown	Very Rare
Immune system disorders		Hypersensitivity reactions including anaphylactic responses[2]	
Respiratory, thoracic and mediastinal disorders		Interstitial lung disease[2]	
Gastrointestinal disorders		Vomiting[2] Acute pancreatitis[2,a] Fatal and non-fatal haemorrhagic and necrotising pancreatitis[2]	

System Organ Class	Uncommon	Unknown	Very Rare
Skin and subcutaneous tissue disorders	Pruritus[2]	Rash[1,2,b] Angioedema[2] Urticaria[2] Cutaneous vasculitis[2] Exfoliative skin conditions including Stevens-Johnson syndrome[2] Bullous pemphigoid[2]	
Musculoskeletal and connective tissue disorders		Arthralgia[2] Myalgia[2] Back pain[2] Arthropathy[2]	
Renal and urinary disorders		Impaired renal function[2] Acute renal failure[2]	
Infections and Infestations			Necrotising fasciitis of the perineum (Fournier's gangrene)[1]

[1] Adverse reaction with dapagliflozin.
[2] Adverse reaction with sitagliptin.
[a] See subsection 'Description of selected adverse reactions' below 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'.

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.

Events of genital infections were reported in 5.5% and 0.6% of patients who received dapagliflozin 10 mg and placebo, respectively, in the 13 study, short-term, placebo-controlled pool. 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). 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 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.

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.

Events of UTI were reported in 4.7% and 3.5% of patients who received dapagliflozin 10 mg and placebo, respectively, in the 13 study, short-term, placebo-controlled pool. 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). 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).

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.

Diabetic ketoacidosis (DKA)

Dapagliflozin

In the DECLARE study 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 special 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 3.

Table 3 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)

	Placebo	Dapagliflozin 10 mg
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 <54 mg/dL 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 <63 mg/dL regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL that does not qualify as a major episode.

[c] Excluding data after rescue.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin (see section 4.4).

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

Sitagliptin

Hypoglycaemia was observed more frequently (frequency 'very common') when sitagliptin was studied with the combination of sulphonylurea and metformin, compared with studies of sitagliptin as monotherapy.

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 m2), 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.

Acute pancreatitis

Sitagliptin

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.

4.9 Overdose

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 600 mg per day for periods of up to 10 days and 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

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. The combination of both agents delivers clinically meaningful reductions in haemoglobin A1c (HbA1c) for improved glycaemic control in patients

with type 2 diabetes mellitus. While sitagliptin has a neutral effect on weight, urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with weight loss.

Dapagliflozin

Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium glucose cotransporter 2 (SGLT2) 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 diastolic function, and preserve renal function. Other effects include an increase in haematocrit and reduction in body weight.
Dapagliflozin improves both fasting and postprandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. 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 greater than 1400 times more selective for SGLT2 *versus* SGLT1, the major transporter in the gut responsible for glucose absorption.

Sitagliptin

Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these 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. These hormones are rapidly inactivated by the enzyme, DPP-4. 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 signaling pathways

involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

5.1 Pharmacodynamic properties

General

Dapagliflozin

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

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume. Urinary volume increases in patients with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.
Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from 0.33 mg/dL to 0.87 mg/dL.

Sitagliptin

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Clinical trial information

Clinical efficacy

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. Additionally, a clinically relevant and statistically significant reduction in mean change from baseline in body weight was seen at Week 24. In a dedicated clinical study of dapagliflozin to evaluate body composition, decrease in weight was mainly attributable to a reduction in body fat mass as measured by DXA.

In two studies of dapagliflozin 10 mg in type 2 diabetes mellitus patients with hypertension, statistically significant reductions in mean seated systolic blood pressure (SBP) were seen in patients treated with dapagliflozin 10 mg combined with other oral antidiabetic and

antihypertensive treatments (an angiotensin converting enzyme inhibitor [ACEi] or angiotensin receptor blocker [ARB] in one study and an ACEi or ARB plus one additional antihypertensive treatment in another study) compared to those treated with placebo at Week 12.

Glycaemic control

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

A total of 452 patients with type 2 diabetes who were drug naive, or who were treated at entry with metformin or a DPP4 inhibitor alone or in combination, and had inadequate glycemic control (HbA1c ≥7.0% and ≤10.0% at randomization), participated in this 24-week, placebo-controlled study with a 24-week extension period to evaluate dapagliflozin co-administered with sitagliptin (a DPP4 inhibitor) 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.

Co-administered with sitagliptin (with and without metformin), dapagliflozin 10 mg provided significant improvements in HbA1c, HbA1c in patients with baseline HbA1c ≥8%, FPG, and body weight compared with the placebo plus sitagliptin (with or without metformin) group at Week 24 (Table 4). 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 the stratum of patients who received dapagliflozin 10 mg plus sitagliptin and metformin (n=113) compared with placebo plus sitagliptin with metformin (n=113).

At Week 48, adjusted mean change from baseline in HbA1c, HbA1c in patients with HbA1c ≥8% at baseline, FPG, PPG, and body weight were −0.30%, −0.72%, −19.7 mg/dL, −43.0 mg/dL, and −2.03 kg, respectively, for patients treated with dapagliflozin 10 mg plus sitagliptin with or without metformin, and 0.38%, 0.26%, 13.5 mg/dL,−12.1 mg/dL, and 0.18 kg for patients treated with placebo plus sitagliptin with or without metformin based on the longitudinal repeated measures analysis excluding data after rescue. At Week 48, for the stratum of patients without metformin, adjusted mean change from baseline in HbA1c for patients treated with dapagliflozin 10 mg plus sitagliptin was 0.00% and placebo plus sitagliptin was 0.85%; and the stratum of patients with metformin, adjusted mean change from baseline in HbA1c for patients treated with dapagliflozin 10 mg plus sitagliptin was −0.44% and placebo plus sitagliptin was 0.15% based on the longitudinal repeated measures analysis excluding data after rescue.

The proportion of patients at Week 24 and Week 48 who were rescued or discontinued for lack of glycemic control (adjusted for baseline HbA1c) was higher on sitagliptin with or without metformin (40.5% and 56.5%, respectively) than on 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 (Full Analysis Set and Strata without or with Metformin)

	Sitagliptin 100 mg					
Efficacy Parameter	**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)	
Change from baseline in HbA1c in patients with baseline HbA1c ≥8% (adjusted mean[‡])	−0.80[¶] (N= 94)	0.03 (N= 99)	−0.81[§]	0.06	−0.79[§]	0.0
FPG (mg/dL)						
Baseline (mean)	161.7	163.1	157.3	161.5	165.9	164.7
Change from baseline at Week 24 (adjusted mean[‡])	−24.1	3.8	−22.0	4.6	−26.2	3.0
Difference from placebo (adjusted mean[‡]) (95% CI)	−27.9[§] (−34.5, −21.4)		−26.6[§] (−36.3, −16.85)		−29.2[§] (−38.0, −20.4)	
Body Weight (kg)						
Baseline (mean)	91.02	89.23	88.01	84.20	93.95	94.17

	Sitagliptin 100 mg					
Efficacy Parameter	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**
	Full Study Population		**without Metformin**		**with Metformin**	
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)						
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[¶] (mg/dL)						
Baseline (mean)	227.8	226.3	225.3	231.2	230.2	221.0
Change from baseline (adjusted mean[‡])	−47.7	−4.8	−46.3	−2.6	−48.9	−7.2
Difference from placebo (adjusted mean[‡]) (95% CI)	−42.9 (−52.1, −33.8)		−43.7 (−55.9, −31.5)		−41.6 (−55.4, −27.8)	

	Sitagliptin 100 mg					
Efficacy Parameter	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**
	Full Study Population		**without Metformin**		**with Metformin**	
Patients with HbA1c decrease ≥ 0.7% (adjusted %)	35.3	16.6	42.8	17.2	28.0	16.0

* LOCF: last observation (prior to rescue for rescued patients) carried forward; including data after rescue for SBP.
† 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 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 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 -21.46 mg/dL and -16.59 mg/dL, 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

Efficacy Parameter	Dapagliflozin 10 mg N=159	Placebo N=161
Difference from placebo (adjusted mean*) (95% CI)	-0.34§ (-0.53, -0.15)	
FPG (mg/dL)		
Baseline (mean)	183.04	173.28
Change from baseline (adjusted mean*)	-21.46	-4.87
Difference from placebo (adjusted mean*) (95% CI)	-16.59§ (-26.73, -6.45)	
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).

Supportive study

Dapagliflozin dual energy X ray absorptiometry in patients with type 2 diabetes mellitus

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. Week 24 was analysed using last observation carried forward (LOCF) analysis including data after rescue.

The improvements in body weight, waist circumference, body-fat mass and visceral adipose tissue observed at Week 24 were sustained at Week 50 and Week 102. There was no change in bone mineral density in either treatment group up to Week 102 (mean decrease from baseline for all anatomical regions <1.0%).

Cardiovascular and Renal Outcomes studies in patients with type 2 diabetes mellitus

Dapagliflozin

Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicenter, randomized, double-blind, placebo-controlled clinical study conducted to determine the effect of FORXIGA compared with placebo on CV 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 dyslipidemia, hypertension or current tobacco use) or established CV disease.

Of 17,160 randomized patients, 6,974 (40.6%) had established CV disease and 10,186 (59.4%) did not have established CV disease. 8,582 patients were randomized to FORXIGA 10 mg and 8,578 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. 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/ m2.

At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 mL/min/1.73 m2, 7.4% of patients had eGFR <60mL/min/1.73 m^2 and 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ratio [UACR] ≥30 to ≤300 mg/g or >300 mg/g, respectively).

Most patients (98%) used one or more diabetic medications at baseline, including metformin (82%), insulin (41%) and sulfonylurea (43%).

The primary endpoints were time to first event of the composite of CV death, myocardial infarction or ischaemic stroke (MACE) and time to first event of the composite of hospitalization for heart failure or CV death. The secondary endpoints were a renal composite endpoint and all-cause mortality.

Major Adverse Cardiovascular Events

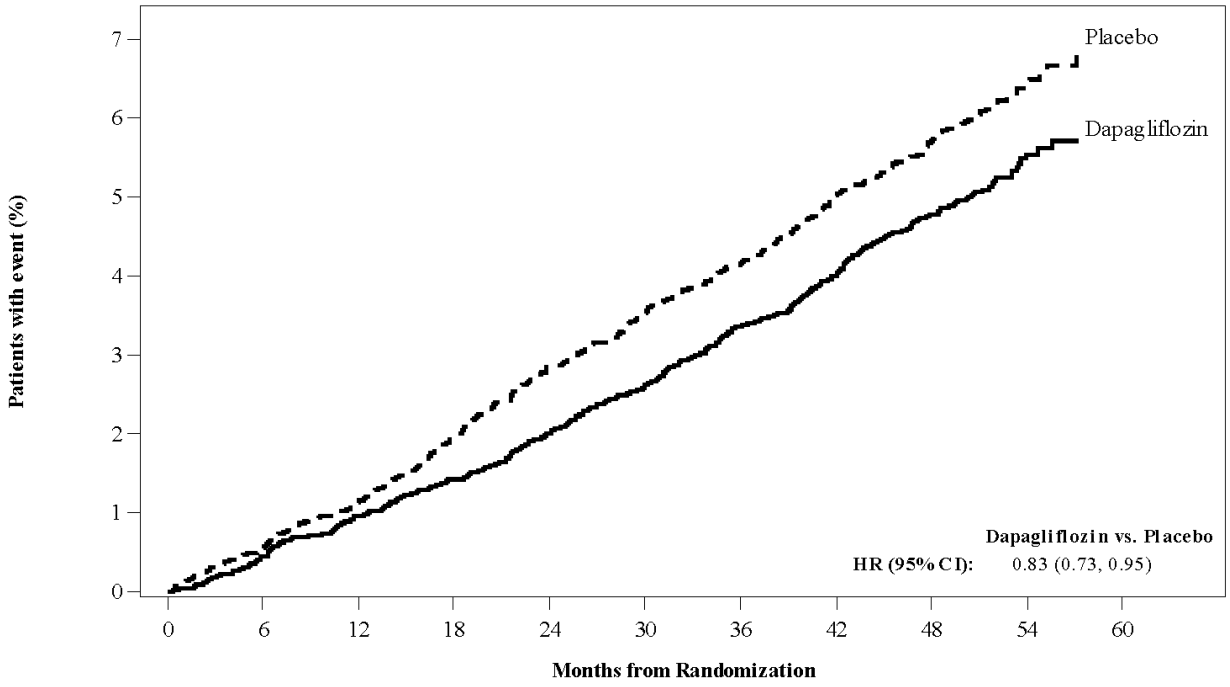
Dapagliflozin 10 mg demonstrated non-inferiority versus placebo for the composite of CV death, myocardial infarction or ischemic stroke (one-sided p <0.001).

Heart Failure or Cardiovascular Death

Dapagliflozin 10 mg demonstrated superiority versus placebo in preventing the composite of hospitalization for heart failure or CV death (Figure 1). The difference in treatment effect was driven by hospitalization for heart failure, with no difference in CV death (Figure 2).

The treatment benefit of FORXIGA over placebo was observed both in patients with and without established CV disease, with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR), and region.

Figure 1 Time to first occurrence of hospitalization for heart failure or cardiovascular death



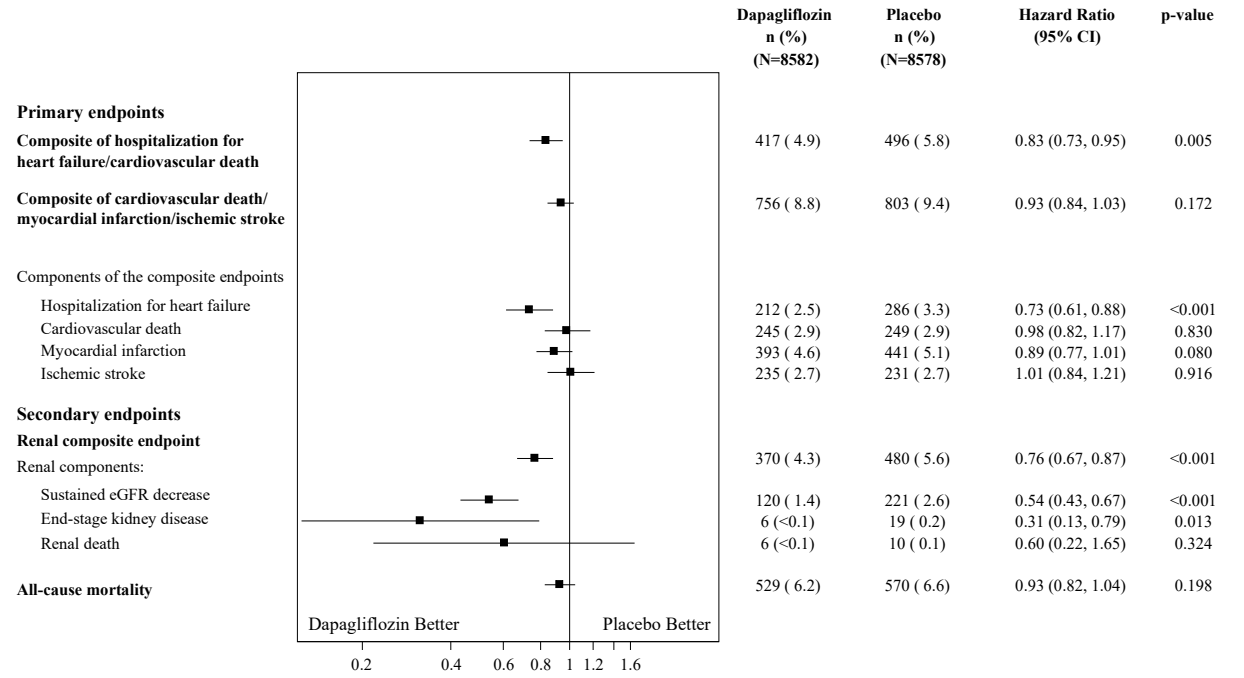
Patients at risk

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.

Results on primary and secondary endpoints are displayed in Figure 2. Superiority of dapagliflozin over placebo was not demonstrated for MACE (p=0.172). The renal composite endpoint and all-cause mortality were therefore not tested as part of the confirmatory testing procedure.

Figure 2 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 m2) and/or renal or CV death.
CI=confidence interval.

Nephropathy

Dapagliflozin reduced the incidence of events of the composite of confirmed sustained eGFR decrease, ESKD, renal or CV death. The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, ESKD and renal death (Figure 2).

The hazard ratio for time to nephropathy (sustained eGFR decrease, end-stage renal disease and renal death) was 0.53 (95% CI 0.43, 0.66) for dapagliflozin versus placebo.

In addition, Dapagliflozin reduced the new onset of sustained albuminuria (hazard ratio 0.79 [95% CI 0.72, 0.87]) and led to greater regression of macroalbuminuria (hazard ratio 1.82 [95% CI 1.51, 2.20]) compared with placebo.

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

After a median follow up of 3 years, 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.

Laboratory findings - dapagliflozin

Haematocrit

In the pool of 13 placebo-controlled studies, increases from baseline in mean haematocrit values were observed in dapagliflozin-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in haematocrit were 2.30% in the dapagliflozin 10 mg group *versus* −0.33% in the placebo group. At Week 102, the mean changes were 2.68% *versus* −0.46%, respectively. By Week 24, haematocrit values >55% were reported in 1.3% of dapagliflozin 10 mg-treated patients *versus* 0.4% of placebo treated patients. Results were similar during the short-term plus long-term phase (the majority of patients were exposed to treatment for more than one year).

Serum inorganic phosphorus

In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin 10 mg-treated patients compared with placebo-treated patients (mean increases of 0.13 mg/dL *versus* −0.04 mg/dL, respectively). Similar results were seen at Week 102. Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥5.6 mg/dL if age 17 65 or ≥5.1 mg/dL if age ≥66) were reported in dapagliflozin 10 mg group *versus* placebo at Week 24 (1.7% *versus* 0.9%, respectively) and during the short-term plus long-term phase (3.0% *versus* 1.6%, respectively). The clinical relevance of these findings is unknown.

Lipids

In the pool of 13 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. 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%. 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%. The ratio between LDL cholesterol and HDL cholesterol decreased for both treatment groups at Week 24.

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

5.2 Pharmacokinetic properties

Dapagliflozin/sitagliptin combination

SIDAPVIA 10mg/100mg tablets are considered to be bioequivalent to co-administration of corresponding doses of dapagliflozin and sitagliptin administered together as single dose individual tablets in healthy subjects in fasted state.

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

The absolute bioavailability of sitagliptin is approximately 87%. Because coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin 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 a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon carbon bond, thereby conferring stability against glucosidase enzymes. The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin is 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounts for 61% of a 50 mg [^{14}C]-dapagliflozin dose and is the predominant drug-related component in human plasma, accounting for 42% (based on AUC [0-12 hour]) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounts for >5% of the total plasma radioactivity. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism is a minor clearance pathway in humans.

Sitagliptin

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination.

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

Elimination

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.

Sitagliptin

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

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein 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 (GFR ≥60 to <90 mL/min) and patients with moderate renal impairment (GFR ≥45 to <60 mL/min), 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 to <45 mL/min), and approximately 4-fold in patients with severe renal

impairment (GFR <30 mL/min), 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.

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.

Sitagliptin

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%). These differences in systemic exposure were considered to not be clinically meaningful.

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

SIDAPVIA is not indicated in paediatric and adolescent patients (see Section 4.2 Posology and method of administration).

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 AUCss in females (n=619) was estimated to be 22% higher than in males (n=634) (90% CI; 117,124).

Sitagliptin

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

Sitagliptin

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.

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

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

Dapagliflozin/sitagliptin combination

No animal studies have been conducted with the combination of dapagliflozin and sitagliptin. The following data are based on the findings from separate nonclinical studies on dapagliflozin and sitagliptin, respectively.

Carcinogenesis, mutagenesis, impairment of fertility

Dapagliflozin

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

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

In a study of fertility and early embryonic development in rats, doses of 15, 75, or 300/210 mg/kg/day dapagliflozin were administered to males (the 300 mg/kg/day dose was lowered to 210 mg/kg/day after 4 days), and doses of 3, 15, or 75 mg/kg/day were administered to females. Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated males or females at any dose tested (at exposure multiples ≤1708× and 998× the MRHD in males and females, respectively). However, at 300/210 mg/kg/day, seminal vesicle and epididymal weights were reduced; sperm motility and sperm counts were reduced; and there were low numbers of morphologically abnormal sperm.

Sitagliptin

A two-year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of combined liver adenoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results in exposures approximately 60 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 100 mg/day based on AUC comparisons. Liver tumors were not observed at 150 mg/kg, approximately 20 times the human exposure at the MRHD. A two-year carcinogenicity study was conducted in male and female mice given oral doses

of sitagliptin of 50, 125, 250, and 500 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 500 mg/kg, approximately 70 times human exposure at the MRHD. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an in vitro cytogenetics assay in CHO, an in vitro rat hepatocyte DNA alkaline elution assay, and an in vivo micronucleus assay.
In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination (approximately 8 weeks total) and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, nondose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison).

Teratogenicity and impairment of early development

Dapagliflozin

Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy and lactation (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

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

In a separate study of prenatal and postnatal development, maternal rats were dosed from gestation day (GD) 6 through PND 21 (also at 1, 15, or 75 mg/kg/day), and pups were indirectly exposed in utero and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups). Increased incidence or severity of renal pelvic dilatation was again observed in adult offspring of treated dams, although only at 75 mg/kg/day (associated maternal and pup dapagliflozin exposures were 1415× and 137×, respectively, the human values at the MRHD). Additional developmental toxicity was limited to dose-related reductions in pup body weights and observed only at doses ≥15 mg/kg/day (associated with pup exposures that are ≥29× the human values at the MRHD). Maternal toxicity was evident only at 75 mg/kg/day and limited to transient reductions in body weight and food consumption at dose initiation. The no-adverse-effect level (NOAEL) for developmental toxicity, 1 mg/kg/day, is associated with a maternal systemic exposure multiple that is approximately 19× the human value at the MRHD.

In additional studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested (20, 60, or 180 mg/kg/day); 180 mg/kg/day is associated with a systemic exposure multiple of approximately 1191× the MRHD. In rats, dapagliflozin was neither embryolethal nor teratogenic

at doses up to 75 mg/kg/day (1441× the MRHD). Doses ≥150 mg/kg/day (≥2344× the human values at the MRHD) were associated with both maternal and developmental toxicities. Maternal toxicity included mortality, adverse clinical signs, and decrements in body weight and food consumption. Developmental toxicity consisted of increased embryo-foetal lethality, increased incidences of foetal malformations and skeletal variations, and reduced foetal body weights. Malformations included a low incidence of great vessel malformations, fused ribs and vertebral centra, and duplicated manubria and sternal centra. Variations were primarily reduced ossifications.

Animal toxicology

Dapagliflozin

Most of the effects observed in pivotal repeat-dose toxicity studies in both rats and dogs were considered to be secondary to pharmacologically mediated increases in urinary glucose, and included decreases in body weights and/or body weight gains, increased food consumption, and increases in urine volumes due to osmotic diuresis. Dapagliflozin was well tolerated when given orally to rats for up to 6 months at doses of ≤25 mg/kg/day (≥346× the human exposures at the MRHD) and in dogs for up to 12 months at doses of ≤120 mg/kg/day (≥3200× the human exposures at the MRHD). Also, single-dose studies with dapagliflozin indicated that the dapagliflozin 3-O-glucuronide metabolite would have been formed in both rat and dog toxicity studies at exposure levels (AUCs) that are greater than, or approximately equal to, anticipated human dapagliflozin 3-O-glucuronide exposures following administration of dapagliflozin at the MRHD. In rats, the most noteworthy nonclinical toxicity finding of increased trabecular bone and tissue mineralization (associated with increased serum calcium) was only observed at high-exposure multiples (≥2100× based on human exposures at the MRHD). Despite achieving exposure multiples of ≥3200× the human exposure at the MRHD, there was no dose-limiting or target-organ toxicities identified in the 12-month dog study.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose, microcrystalline
Mannitol
Calcium hydrogen phosphate
Croscarmellose sodium
Crospovidone
Sodium stearyl fumarate
Magnesium stearate

Film-coating:

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to expiry date on the outer carton.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Supplied in Aluminium / Aluminium foil blister packs in cartons of 28 tablets (i.e 14 tablets per blister x 2 blisters).

6.6 Instructions for use, handling and disposal

No special requirements.

Product Owner

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United Kingdom

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