Proposed packaging material		
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Submission	☒NDA ☐Renewal ☐Variation change detail no.: RO-Primary Event-0001354	
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Reference	☒CDS version: VV-RIM-04940919 CPIL version: N/A	☐SmPC country/version/date:USPI (2020) ☐GRL approval:N/A
Name & Date	YS (27 May 2025)	

SIDAPVIA 10 mg/100 mg
DAPAGLIFLOZIN PROPANEDIOL / SITAGLIPTIN PHOSPHATE MONOHYDRATE
FILM COATED TABLETS

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 12.3 mg dapagliflozin propanediol and 100 mg sitagliptin as 128.5 mg sitagliptin phosphate monohydrate.

For excipients, see section 6.1.

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.

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). Renal function should be evaluated prior to initiation of SIDAPVIA and periodically thereafter.

Hepatic impairment

SIDAPVIA may be used in patients with mild to moderate hepatic impairment. There is limited experience in patients with severe hepatic impairment, therefore, care should be exercised when SIDAPVIA is used in this population (see section 5.2).

Paediatric and adolescent patients

SIDAPVIA is not indicated for use in pediatrics and adolescent patients. Dapagliflozin and sitagliptin have not been studied in paediatric patients aged 0 to less than 18 years. Sitagliptin should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy.

Elderly patients

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).

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 and 4.8).

4.4 Special warnings and special precautions for use

General

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

Urinary tract infections

Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis.

Use in patients at risk for volume depletion and/or hypotension

For patients receiving dapagliflozin, In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g.

physical examination, blood pressure measurements, laboratory tests including electrolytes) is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.

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

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.

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 and 4.8).

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 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

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).

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).

4.5 Interaction with other medicinal products and other forms of interaction

Dapagliflozin and sitagliptin

The lack of pharmacokinetic interaction between dapagliflozin and sitagliptin was demonstrated in a clinical 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 mediate 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.

Effect of other medicinal products on dapagliflozin

Interaction studies conducted in healthy subjects, using mainly a single dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin. 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 55% 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.
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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).

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

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

Sitagliptin

Effect of other drugs on sitagliptin
Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end stage kidney disease (ESKD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESKD. The effect of potent CYP3A4 inhibitors in the setting of renal impairment has not been assessed in a clinical study.

In vitro transport studies showed that sitagliptin is a substrate for P-gp and OAT3. OAT3 mediated transport of sitagliptin was inhibited in vitro by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated in vivo.

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-gp, 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 changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other P-gp inhibitors.

Effect of sitagliptin on other drugs

Digoxin: There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (Cmax, 18%) of digoxin with the co- administration of 100 mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or sitagliptin is recommended.

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.

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.

Fertility

Dapagliflozin/sitagliptin combination

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
However, when driving or operating machines, it should be taken into account that dizziness has been reported with sitagliptin.

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).

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
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 necrotizing pancreatitis[2]
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]

[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'.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via:

Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan

Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika,

Prekursor dan Zat Adiktif

Badan Pengawas Obat dan Makanan

Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

Email: pv-center@pom.go.id

Website: https://e-meso.pom.go.id/ADR

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 *(This information is based on studies related to the innovator of 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.

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 *(This information is based on studies related to the innovator of Sitagliptin)*
Sitagliptin is an oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP4) inhibitors. The improvement in glycaemic control observed with this medicinal product may be mediated 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 such that 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 enhanced as glucose rises above normal concentrations. Further, 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. 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. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulphonylureas, which increase insulin secretion even when glucose levels are low and can lead to hypoglycaemia in patients with type 2 diabetes mellitus and in normal subjects. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP4 and does not inhibit the closely-related enzymes DPP8 or DPP9 at therapeutic concentrations.

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 *(This information is based on studies related to the innovator of 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.

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%, 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.

At Week 48, based on the longitudinal repeated measures analysis excluding data after rescue, adjusted mean change from baseline in HbA1c, HbA1c in patients with HbA1c ≥8% at baseline, FPG, 2-hour postprandial glucose (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. The mean reduction from baseline in HbA1c for patients treated with dapagliflozin 10 mg plus sitagliptin, compared with patients treated with placebo plus sitagliptin was 0.68% (nominal $p<0.0001$) 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 for 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%.

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 3 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)	

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 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 (mg/dL)						
Baseline (mean)	161.7	163.1	157.3	161.5	165.9	164.7
Change from baseline (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
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)	

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†
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)	
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; 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).

For efficacy and safety results from individual clinical studies of dapagliflozin and sitagliptin, please refer to the information in the SPC for either dapagliflozin or sitagliptin.

Glycaemic control in special populations

Use in patients with type 2 diabetes mellitus and hypertension Dapagliflozin

In a pre-specified pooled analysis of 13 placebo-controlled studies, 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 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.

In a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m2, treatment with dapagliflozin demonstrated reductions in seated systolic blood pressure at week 24: -4.8 mmHg compared to -1.7 mmHg for placebo ($p < 0.05$).

Use in patients with type 2 diabetes mellitus and renal impairment Dapagliflozin

Moderate renal impairment CKD 3A (eGFR ≥ 45 to < 60 mL/min/1.73 m2)

The efficacy of dapagliflozin was assessed in a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m2 who had inadequate glycaemic control on usual care. Treatment with dapagliflozin resulted in reductions in HbA1c and body weight compared with placebo (Table 7).

Table 4. Results at week 24 of a placebo-controlled study of dapagliflozin in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m²

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

[a] Metformin or metformin hydrochloride were part of the usual care in 69.4% and 64.0% of the patients for the

dapagliflozin and placebo groups, respectively.
[b] Least squares mean adjusted for baseline value
[c] Derived from least squares mean adjusted for baseline value
[*] p<0.001

Clinical safety

Events related to decreased renal function - dapagliflozin

Adverse drug reactions related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). In the 13-study safety pool, this grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR ≥ 60 mL/min/1.73m2) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR ≥ 30 and < 60 mL/min/1.73m2 (18.5% dapagliflozin 10 mg vs 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤ 44 micromoles/L (≤ 0.5 mg/dL) from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

In the DAPA-CKD study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial (day 14) decrease in mean eGFR was 4.0 mL/min/1.73 m2 in the dapagliflozin group and 0.8 mL/min/1.73 m2 in the placebo group. At 28 months, change from baseline in eGFR was 7.4 mL/min/1.73 m2 in the dapagliflozin group and 8.6 mL/min/1.73 m2 in the placebo group.

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 co- administration in the fasted state in healthy subjects.

Geometric mean ratios and corresponding 90% CIs for all primary PK parameters of dapagliflozin and sitagliptin were contained well within the bioequivalence acceptance limit of 80-125%, demonstrating that bioequivalence was achieved between the SIDAPVIA 10 mg/100 mg tablet and dapagliflozin 10 mg + sitagliptin 100 mg co-administered individual tablets.

Between-subject variability (gCV%) in PK exposures was up to approximately 30% and 25% for dapagliflozin Cmax and AUCs, respectively, and up to approximately 32% and 20% for sitagliptin Cmax and AUCs, respectively, and similar between treatments.

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 *(This information is based on studies related to the innovator of sitagliptin)*

Following 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, mean plasma AUC of sitagliptin was 8.52 µM•hr, C_{max} was 950 nM. 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.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution

Dapagliflozin

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

Sitagliptin *(This information is based on studies related to the innovator of 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 *(This information is based on studies related to the innovator of 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.

In vitro data showed that sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

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 *(This information is based on studies related to the innovator of 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. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. In vitro, sitagliptin did not inhibit OAT3
(IC50=160 µM) or P-gp (up to 250 µM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of P-gp.

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 (This information is based on studies related to the innovator of 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. No dose adjustment is required for patients with severe hepatic impairment.

Sitagliptin (This information is based on studies related to the innovator of 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 (This information is based on studies related to the innovator of 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

Pharmacokinetics in the paediatric population have not been studied.

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 (This information is based on studies related to the innovator of 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 (This information is based on studies related to the innovator of 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 (This information is based on studies related to the innovator of 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.

Dapagliflozin

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and ertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.

Reproductive and development toxicity

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.

Sitagliptin *(This information is based on studies related to the innovator of Sitagliptin)*

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 tumours 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 tumours 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, non-dose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison)

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 blister strip or outer carton.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Aluminium/Aluminium blister.

6.6 Instructions for use, handling and disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

PACK SIZE

Box, 2 blisters @ 14 film-coated tablets, Reg No: DKIXXXXXXXXXXXX

Golongan Obat Keras
HARUS DENGAN RESEP DOKTER

Manufactured by:
SK Chemicals Co, Ltd

Cheongju-si
Republic of Korea

Released by:
AstraZeneca AB
Sodertälje
Sweden

Imported by:
PT. AstraZeneca Indonesia,
Cikarang, Bekasi – Indonesia

DATE OF REVISION
27 May 2025
Document Number : VV-RIM-07374278

Proposed packaging material		
Code	Sidapvia 10/100 FCT-PIL-01.02	
Submission	☒NDA ☐Renewal ☐Variation change detail no.: RO-Primary Event-0001354	
Code of previous version	N/A	
Changes	New FDC Sitagliptin and Dapagliflozin	
Reference	☒CDS version: Doc ID-005063093 CPIL version: N/A	☐SmPC country/version/date:USPI (2020) ☐GRL approval:N/A
Name & Date	YS (27 May 2025)	

Informasi Obat untuk Pasien
SIDAPVIA 10 mg/100 mg
Dapagliflozin Propanediol / Sitagliptin Phosphate Monohydrate
Tablet Salut Selaput

Baca seluruh bagian brosur ini dengan cermat sebelum Anda mengonsumsi obat ini karena berisi informasi yang penting untuk Anda.

- Simpan brosur ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan diberikan kepada orang lain. Obat ini dapat membahayakan mereka, sekalipun jika gejala-gejala penyakit mereka sama dengan Anda
- Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat. Termasuk segala bentuk efek samping yang tidak tercantum di dalam brosur ini. Lihat bagian 4.

Isi brosur ini