

1. Name of the medicinal product:

DAPAGOOD S 100 (Dapagliflozin 10mg and Sitagliptin 100mg Tablets)

2. Qualitative and quantitative composition

Each Tablet contains:

Dapagliflozin propanediol monohydrate

Eq. to Dapagliflozin 10

mg Sitagliptin phosphate monohydrate

USP

Eq. to Sitagliptin 100 mg

Excipients q.s

3. PHARMACEUTICAL FORM

Film Coated Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DAPAGOOD S 100 used alone or together with other diabetes medicines to control blood sugar and avoid long-term complications. It also reduces the risk of heart attack, heart failure or other cardiovascular events.

4.2 Posology and method of administration

Posology

The dosage of DAPAGOOD S 100 should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 10 mg dapagliflozin and 100 mg sitagliptin. Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

Method of administration

DAPAGOOD S 100 can be taken with or without food.

4.3 Contraindications

DAPAGOOD S 100 is contraindicated in patients with:

Patients with a history of hypersensitivity reaction to the Dapagliflozin or Sitagliptin or to any of the excipients.

Patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m², severe renal impairment, end-stage renal disease (ESRD) or patients on dialysis.

4.4 Special warnings and precautions for use

Volume depletion

Before initiating DAPAGOOD S 100, assess volume status and renal function in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics.

Monitor for signs and symptoms during therapy.

Ketoacidosis in Patients with Diabetes Mellitus

Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue this combination, evaluate and treat promptly. Before initiating DAPAGOOD S 100, consider risk factors for ketoacidosis. Patients on this combination may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis.

Urosepsis and Pyelonephritis

Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated. Hypoglycemia

Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with this combination.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Serious, life-threatening cases have occurred in patients with diabetes, both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment.

Genital Mycotic Infections

Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat if indicated.

Pancreatitis

There have been post marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue DAPAGOOD S 100.

Heart failure

An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of this combination prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of DAPAGOOD S 100.

Assessment of renal function

There have been post marketing reports of acute renal failure, sometimes requiring dialysis. Dosage adjustment is recommended in patients with

moderate or severe renal insufficiency and in patients with ESRD. Assessment of renal function is recommended prior to initiating DAPAGOOD S 100 and periodically thereafter.

Hypoglycemia

There is an increased risk of hypoglycemia when dapagliflozin and sitagliptin is added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. Consider lowering the dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia.

Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication.

A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving this combination. If bullous pemphigoid is suspected, DAPAGOOD S 100 should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Hypersensitivity reactions

There have been post marketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin/ dapagliflozin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop DAPAGOOD S 100, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes.

Macrovascular outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with combination of dapagliflozin and sitagliptin.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other medicinal products and other forms of interaction

Digoxin

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C_{max}, 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 this combination is recommended.

Insulin Secretagogues or Insulin

Coadministration of this combination with an insulin secretagogue (e.g.,

sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia. Positive Urine Glucose Test

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

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

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.

Use alternative methods to monitor glycemic control.

4.6 Pregnancy and lactation

Pregnant Women

Risk Summary

There are no adequate and well-controlled studies in pregnant women with dapagliflozin and sitagliptin or its individual components; therefore, the safety of dapagliflozin and sitagliptin in pregnant women is not known. DAPAGOOD S 100 should be used during pregnancy only if clearly needed.

Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. In a prenatal and postnatal development study, dapagliflozin was administered to maternal rats from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed in utero and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in 21-day-old pups offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415-times and 137-times, respectively, the human values at the 10 mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at greater or equal to 29-times the 10 mg clinical dose (based on AUC). No adverse effects on developmental endpoints were noted at 1 mg/kg/day (19-times the 10 mg clinical dose, based on AUC). These outcomes occurred with drug exposure during periods of renal development in rats that corresponds to the late second and third trimester of human development. In embryofetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy. In rats, dapagliflozin was neither embryoletal nor teratogenic at doses up to 75 mg/kg/day (1441-times the 10 mg clinical dose, based on AUC).

Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only at higher dosages, equal to or greater than 150 mg/kg (more than 2344-times the 10 mg clinical dose, based on AUC), which were associated with maternal toxicity. No developmental toxicities were observed in rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose, based on AUC).

The data are based on findings in studies performed with Dapagliflozin and Sitagliptin individually.

Lactating Women

Risk Summary

No studies in lactating animals have been conducted with the combined components of dapagliflozin and sitagliptin. In studies performed with the individual components, both dapagliflozin and sitagliptin are secreted in the milk of lactating rats. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DAPAGOOD S 100 is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Dapagliflozin and Sitagliptin has no or negligible influence on the ability to drive and use machines.

Patients should be alerted to the risk of hypoglycaemia when the combination is use with a sulfonylurea or insulin.

4.8 Undesirable effects

Dapagliflozin

The most common adverse reactions associated with dapagliflozin (5% or greater incidence) were female genital mycotic infections, nasopharyngitis, and urinary tract infections.

Laboratory tests

Increases in Serum Creatinine and Decreases in eGFR

Initiation of SGLT2 inhibitors, including dapagliflozin causes a small increase in serum creatinine and decrease in eGFR. In patients with normal or mildly impaired renal function at baseline, these changes in serum creatinine and eGFR generally occur within weeks of starting therapy and then stabilize. Increases that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury. The acute effect on eGFR reverses after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with dapagliflozin.

Increase in Hematocrit

In the pool of 13 placebo-controlled studies of glycemic control, increases from baseline in mean hematocrit 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 hematocrit were -0.33% in the placebo group and 2.30% in the dapagliflozin 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of dapagliflozin 10 mg-treated patients. Increase in Low-Density Lipoprotein Cholesterol

In the pool of 13 placebo-controlled studies of glycemic control, changes from baseline in mean lipid values were reported in dapagliflozin-treated patients compared to placebo-treated patients. Mean percent changes from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol, and -1.0% versus 2.9% for LDL cholesterol in the placebo and dapagliflozin 10 mg groups, respectively. In the DECLARE study, mean changes from baseline after 4 years were

0.4 mg/dL versus -4.1 mg/dL for total cholesterol, and -2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in dapagliflozin-treated and the placebo groups, respectively.

Decrease in Serum Bicarbonate

In a study of concomitant therapy of dapagliflozin 10 mg with exenatide extended-release (on a background of metformin), four patients (1.7%) on concomitant therapy had a serum bicarbonate value of less than or equal to 13 mEq/L compared to one each (0.4%) in the dapagliflozin and exenatide-extended-release treatment groups.

Sitagliptin

Adverse reactions reported in 35% of patients treated with sitagliptin and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. In the add on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with sitagliptin compared to placebo.

Laboratory tests

Across clinical studies, the incidence of laboratory adverse reactions was similar in patients treated with sitagliptin 100 mg compared to patients treated with placebo. A small increase in white blood cell count (WBC) was observed due to an increase in neutrophils. This increase in WBC (of approximately 200 cells/microL vs placebo, in four pooled placebo-controlled clinical studies, with a mean baseline WBC count of approximately 6600 cells/microL) is not considered to be clinically relevant. In a 12-week study of 91 patients with chronic renal insufficiency, 37 patients with moderate renal insufficiency were randomized to sitagliptin 50 mg daily, while 14 patients with the same magnitude of renal impairment were randomized to placebo. Mean increases in serum creatinine were observed in patients treated with sitagliptin and in patients treated with placebo. The clinical significance of this added increase in serum creatinine relative to placebo is not known.

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 Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org/>

4.9 Overdose

Dapagliflozin

There were no reports of overdose during the clinical development program for dapagliflozin. It is also reasonable to employ supportive measures as dictated by the patient's clinical status.

The removal of dapagliflozin by hemodialysis has not been studied. Sitagliptin

During controlled clinical trials in healthy subjects, single doses of up to 800 mg Sitagliptin were administered. Maximal mean increases in QTc of 8.0

msec were observed in one study at a dose of 800 mg sitagliptin, a mean effect that is not considered clinically important. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for 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 as dictated by the patient's clinical status. Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session.

Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

DAPAGOOD S 100 combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and dapagliflozin, a sodium glucose cotransporter 2.

Dapagliflozin

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity.

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 insulintropic 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.

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.

Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day at Week 12. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg.

This urinary glucose excretion with dapagliflozin also results in increases in urinary volume. After discontinuation of dapagliflozin, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg dose.

Cardiac electrophysiology

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15-times the recommended maximum dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50-times the recommended maximum dose) of dapagliflozin in healthy subjects.

Sitagliptin

In patients with type 2 diabetes, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.

Cardiac Electrophysiology

In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800-mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline at 3 hours postdose was 8.0 msec. This increase is not considered to be clinically significant. At the 800-mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100-mg dose. In patients with type 2 diabetes administered sitagliptin 100 mg (N=81) or sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

5.2 Pharmacokinetic properties

Absorption

Dapagliflozin

Following oral administration of dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hours under fasting state. The C_{max} and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%.

Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs 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 and dapagliflozin can be administered with or without food.

Sitagliptin

After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours postdose. The absolute bioavailability of sitagliptin is approximately 87%. Co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with 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 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Metabolism

Dapagliflozin

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg -dapagliflozin dose and is the predominant drug-related component in human plasma.

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 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 the renal

pathway. Following a single 50 mg dose of -dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

Sitagliptin

Following administration of an oral 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 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-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. Special Populations

Effect on Age, body weight, gender and race on pharmacokinetics

Dapagliflozin

Based on a population pharmacokinetic analysis, age, gender, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of dapagliflozin and thus, no dose adjustment is recommended.

Sitagliptin

Based on a population pharmacokinetic analysis or a composite analysis of available pharmacokinetic data, BMI, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. When the effects of age on renal function are taken into account, age alone did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Pediatric

Pharmacokinetics in the pediatric population have not been studied for dapagliflozin or sitagliptin.

Patients with Renal

Impairment Dapagliflozin

At steady-state (20 mg once daily dapagliflozin for 7 days), patients with type 2 diabetes with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of dapagliflozin that were 45%, 2.04-fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes mellitus with normal renal function. Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour urinary glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes mellitus and mild, moderate, and severe renal impairment was 42%,

80%, and 90% lower, respectively, than in patients with type 2 diabetes mellitus with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known.

Sitagliptin

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to less than 45 mL/min/1.73 m², and an approximately 4-fold increase was observed in patients with severe renal impairment, including patients with ESRD on hemodialysis, as compared to normal healthy control subjects.

Hepatic

Impairment

Dapagliflozin

In subjects with mild and moderate hepatic impairment (Child-Pugh classes A and B), mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, as compared to healthy matched control subjects following single-dose administration of 10 mg dapagliflozin. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh class C), mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls.

Sitagliptin

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

5.3 Preclinical safety data

No animal studies have been conducted with the combined products in Dapagliflozin and sitagliptin to evaluate effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sr. No.	Name of Excipient
1	Microcrystalline Cellulose
2	Dibasic Calcium phosphate
3	Purified water
4	Crospovidone
5	Low Substituted Hydroxy propyl cellulose-LH 11
6	Magnesium Stearate
7	White film coat
8	PEG 400

9	Isopropyl Alcohol
10	Dichloromethane

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container

10 tablets are packed in ALU-ALU blister, such 3 blisters are packed in one carton with insert coded with batch number, manufacturing date and expiry date.

6.6 Special precautions for disposal and other handling

Not applicable

7. Marketing Authorisation Holder

ZAIN PHARMA LIMITED

Plot No: 209/13741, Colchester Park,
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8. Marketing Authorization Number:

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9. Date of First <Registration> / Renewal of the <Registration>

2026 May 16

10. Date of Revision of the Text:

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