

Prescribing Information

For the use of a Registered Medical Practitioner, or a Hospital, or a Laboratory only

DAPAGLIFLOZIN 10 MG AND SITAGLIPTIN PHOSPHATE 100 MG TABLETS



1. GENERIC NAME
Dapagliflozin 10 mg and Sitagliptin Phosphate 100 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Dapagliflozin 10 mg and Sitagliptin Phosphate 100 mg Tablets
Each film coated tablet contains:
Dapagliflozin Propanediol USP
eq. to Dapagliflozin 10 mg
Sitagliptin Phosphate Monohydrate IP 128.5 mg
eq. to Sitagliptin 100 mg
Colours: Ferric Oxide Yellow USP-NF & Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH
Oral dosage form (Tablets)
Dapagliflozin 10 mg and Sitagliptin Phosphate 100 mg

4. CLINICAL PARTICULARS
4.1 Therapeutic indication
It is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.

4.2 Posology and method of administration
The recommended dose of Fixed dose combination of Dapagliflozin and Sitagliptin Phosphate is 1 tablet orally once daily with or without food or as prescribed by the doctor. Swallow whole tablet with a glass of water, do not chew, break, or crush it.
The renal function monitoring of Dapagliflozin and Sitagliptin Phosphate Tablet and periodically thereafter.
For patients with an estimated glomerular filtration rate [eGFR] greater than or equal to 45 mL/min/1.73 m² to less than 90 mL/min/1.73 m², no dosage adjustment for Dapagliflozin and Sitagliptin Phosphate is required.
Dosage adjustment for Dapagliflozin and Sitagliptin Phosphate Tablet is required for patients with moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 m² to less than 45 mL/min/1.73 m²), the dose of Sitagliptin is 50 mg once daily.
Initiation of Dapagliflozin and Sitagliptin Phosphate Tablet is not recommended for patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²) and contraindicated in patients with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis.

4.3 Contraindications
History of a hypersensitivity reaction to Dapagliflozin and Sitagliptin, such as anaphylaxis or angioedema.
Severe renal impairment, end-stage renal disease (ESRD), or patients on dialysis.

4.4 Special warnings and precautions for use
Dapagliflozin
Ketocidosis in Patients with Diabetes Mellitus
Reports of ketocidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including Dapagliflozin. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketocidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Fatal cases of ketocidosis have been reported in patients taking Dapagliflozin. Dapagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus.
Patients treated with Dapagliflozin who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketocidosis regardless of presenting blood glucose levels as ketocidosis associated with Dapagliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketocidosis is suspected, Dapagliflozin should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketocidosis may require insulin, fluid, and carbohydrate replacement.
In many of the post-marketing reports, and particularly in patients with type 1 diabetes, the presence of ketocidosis was not immediately recognized, and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketocidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors contributing to ketocidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.
Before initiating Dapagliflozin, consider factors in the patient history that may predispose to ketocidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. For patients who undergo scheduled surgery, consider temporarily discontinuing Dapagliflozin for at least 3 days prior to surgery. Consider monitoring for ketocidosis and temporarily discontinuing Dapagliflozin in other clinical situations known to predispose to ketocidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketocidosis are resolved prior to restarting Dapagliflozin. Educate patients on the signs and symptoms of ketocidosis and instruct patients to discontinue Dapagliflozin and seek medical attention immediately if signs and symptoms occur.

Volume Depletion
Dapagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including Dapagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating Dapagliflozin in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension, and renal function after initiating therapy.

Urosepsis and Pyelonephritis
Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including Dapagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with Dapagliflozin.

Neurotizing Fasciitis of the Perineum (Fournier's Gangrene)
Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare and serious life-threatening necrotizing infection requiring urgent surgical intervention, have been reported in patients with post-marketing reports in patients with diabetes mellitus receiving SGLT2 inhibitors, including Dapagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries and death.
Patients treated with Dapagliflozin presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue Dapagliflozin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycaemic control.

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 appropriately.

Sitagliptin
Pancreatitis
There have been post marketing reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotizing pancreatitis, in patients taking Sitagliptin. After initiation of Sitagliptin, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Sitagliptin should promptly be discontinued, and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin.

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 inhibitors.
These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of Sitagliptin 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 Sitagliptin.

Acute Renal Failure
There have been post marketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal impairment, some of whom were prescribed inappropriate doses of sitagliptin. A return to baseline levels of renal impairment has been observed with supportive treatment and discontinuation of potentially causative agents. Consideration can be given to cautiously reinitiating Sitagliptin if another etiology is deemed likely to have precipitated the acute worsening of renal function.
Assessment of renal function is recommended prior to initiating Sitagliptin and periodically thereafter. A dosage adjustment is recommended in patients with moderate or severe renal impairment and in patients with ESRD requiring hemodialysis or peritoneal dialysis.

Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues
When Sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

Hypersensitivity Reactions
There have been post marketing reports of serious hypersensitivity reactions in patients treated with Sitagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with Sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue Sitagliptin, assess for other potential causes for the event, and institute alternative treatment for diabetes. Angioedema has also been reported with other DPP-4 inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Sitagliptin.

Severe and Disabling Arthralgia
There have been post marketing 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
Post marketing 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 Sitagliptin. If bullous pemphigoid is suspected, Sitagliptin should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Sitagliptin or any other anti-diabetic drug.

4.5 Drug Interactions
Dapagliflozin
Clinically Relevant Interactions with Dapagliflozin

Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia may be increased when Dapagliflozin is used concomitantly with insulin or insulin secretagogues (e.g., sulfonylurea)
Intervention	Concomitant use may require lower doses of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.

Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention	Monitor serum lithium concentration more frequently during Dapagliflozin initiation and dosage changes.

Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycaemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycaemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycaemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycaemic control.

Sitagliptin
Insulin Secretagogues or Insulin
Coadministration of Sitagliptin 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.

4.6 Use in special populations
Dapagliflozin
Pregnancy
Risk Summary
Based on animal data showing adverse renal effects, Dapagliflozin is not recommended during the second and third trimesters of pregnancy. Limited data with Dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes and untreated heart failure in pregnancy.
In animal studies, adverse renal pelvic and tubule dilations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose.
The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryofetal risk
Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketocidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data
Animal Data
Dapagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilations at all dose levels. Exposure at the lowest dose tested was 15-times the 10 mg clinical dose (based on AUC). The renal pelvic and tubular dilations observed in juvenile animals did not fully reverse within a 1-month recovery period. 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 dilation 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 embryolethal 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 fetuses (structural abnormalities and reduced body weight) occurred only at higher doses, 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).

Lactation
Risk Summary
There is no information regarding the presence of dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Dapagliflozin is present in the milk of lactating rats. However, due to species specific differences in lactation physiology, the clinical relevance of these data are not clear. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in breastfed infants, advise women that use of Dapagliflozin is not recommended while breastfeeding.

Data
Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilations) during maturation.

Pediatric Use
Safety and effectiveness of Dapagliflozin in pediatric patients under 18 years of age have not been established.

Geriatric Use
No Dapagliflozin dosage change is recommended based on age. A total of 1424 (24%) of the 5936 Dapagliflozin-treated patients were 65 years and older and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical studies assessing the efficacy of Dapagliflozin in improving glycaemic control in type 2 diabetes mellitus. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with Dapagliflozin had adverse reactions of hypotension.
In both the DAPA-HF and DAPA-CKD studies, safety and efficacy were similar for patients age 65 years and younger and those older than 65. In the DAPA-HF study, 2714 (57%) out of 4744 patients with HFEF were older than 65 years. In the DAPA-CKD study, 1818 (42%) out of 4304 patients with CKD were older than 65 years.

Renal Impairment
Dapagliflozin was evaluated in 4304 patients with chronic kidney disease (eGFR ≥25 to 75 mL/min/1.73 m²) in the DAPA-CKD study. Dapagliflozin was also evaluated in 1926 patients with an eGFR of 30 to 60 mL/min/1.73 m² in the DAPA-HF study. The safety profile of Dapagliflozin across eGFR subgroups in these studies was consistent with the known safety profile. Dapagliflozin was evaluated in two clinical studies that included patients with type 2 diabetes mellitus with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m²), and an eGFR of 30 to less than 45 mL/min/1.73 m², respectively. Patients with diabetes and renal impairment using Dapagliflozin may be more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion. In the study of patients with an eGFR 30 to less than 60 mL/min/1.73 m², 13 patients receiving Dapagliflozin experienced bone fractures compared to none receiving placebo. Use of Dapagliflozin for glycaemic control in patients without established CV disease or CV risk factors is not recommended when eGFR is less than 45 mL/min/1.73 m².
Efficacy and safety studies with Dapagliflozin did not enroll patients with an eGFR less than 25 mL/min/1.73 m². Dapagliflozin is contraindicated in patients on dialysis.

Hepatic Impairment
No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefit-risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population.

Sitagliptin
Pregnancy
Risk Summary
The limited available data with Sitagliptin in pregnant women are not sufficient to inform a drug associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes and untreated heart failure in pregnancy. There are risks to the mother and fetus associated with poorly controlled diabetes and untreated heart failure in pregnancy. Organogenesis at oral doses up to 30-times and 20-times, respectively, the 100 mg clinical dose, based on AUC.
The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a Hemoglobin A1c >7% and has been reported to be as high as 20-25% in women with a Hemoglobin A1c >10%. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketocidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data
Animal Data
In embryo-fetal development studies, sitagliptin administered to pregnant rats and rabbits during organogenesis (gestation day 6 to 20) did not adversely affect developmental outcomes at oral doses up to 250 mg/kg (30-times the 100 mg clinical dose) and 125 mg/kg (20-times the 100 mg clinical dose), respectively, based on AUC. Higher doses in rats associated with maternal toxicity increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100-times the clinical dose, based on AUC. Placental transfer of sitagliptin was observed in pregnant rats and rabbits.
Sitagliptin administered to female rats from gestation day 6 to lactation day 21 caused no functional or behavioral toxicity in offspring of rats at doses up to 1000 mg/kg.

Lactation
Risk Summary
There is no information regarding the presence of sitagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Sitagliptin is present in rat milk and therefore possibly present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sitagliptin and any potential adverse effects on the breastfed infant from Sitagliptin or from the underlying maternal condition.

Data
Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1.

Pediatric Use
The safety and effectiveness of Sitagliptin have not been established in pediatric patients.
Three 20-week double-blind, placebo-controlled studies each with 34-week extensions were conducted to evaluate the efficacy and safety of sitagliptin in 410 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes, with or without insulin therapy (HbA1c 6.5-10% for patients not on insulin, HbA1c 7-10% for patients on insulin). At study entry, patients in study 1 were not treated with oral antihyperglycemic agents; patients in studies 2 and 3 were on maximally tolerated metformin therapy. The primary efficacy endpoint was the change from baseline in HbA1c after 20 weeks of therapy. The pre-specified primary efficacy analyses included data from study 1 and pooled data from studies 2 and 3, regardless of glycaemic rescue or treatment discontinuation.
In both efficacy analyses, the effect of treatment with sitagliptin was not significantly different from placebo. In study 1, the mean baseline HbA1c was 7.5%, and 12% of patients were on insulin therapy. At week 20, the change from baseline in HbA1c in patients treated with Sitagliptin (N=95) was 0.06% compared to 0.23% in patients treated with placebo (N=95), a difference of -0.17% (95% CI: -0.62, 0.28). In studies 2 and 3, the mean baseline HbA1c was 8.0%, 15% of patients were on insulin and 72% were on metformin HCl doses of greater than 1,500 mg daily. At week 20, the change from baseline in HbA1c in patients treated with sitagliptin (N=107) was -0.23% compared to 0.09% in patients treated with placebo (N=113), a difference of -0.33% (95% CI: -0.70, 0.05).

Geriatric Use
Of the total number of subjects (N=3884) in pre-approval clinical safety and efficacy studies of Sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. There were no differences in safety or effectiveness between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out. Because sitagliptin is substantially excreted by the kidney, and because aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients.

4.7 Effects on ability to drive and use machines

Dapagliflozin

Dapagliflozin has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

Sitagliptin

Sitagliptin has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported. In addition, patients should be alerted to the risk of hypoglycaemia when sitagliptin is used in combination with a sulphonylurea or with insulin.

4.8. Undesirable effects

Dapagliflozin

The following important adverse reactions are described below and elsewhere in the labeling:

- Ketocidosis in Patients with Diabetes Mellitus
- Volume Depletion
- Urosepsis and Pyelonephritis
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Genital Mycotic Infections

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Dapagliflozin has been evaluated in clinical trials in patients with type 2 diabetes mellitus, in patients with heart failure, and in patients with chronic kidney disease. The overall safety profile of Dapagliflozin was consistent across the studied indications. Severe hypoglycemia and diabetic ketocidosis (DKA) were observed only in patients with diabetes mellitus.
Clinical Trials in Patients with Type 2 Diabetes Mellitus
Pool of 12 Placebo-Controlled Studies for Dapagliflozin 5 and 10 mg
The data in Table 1 is derived from 12 placebo-controlled studies ranging from 12 to 24 weeks. In 4 studies Dapagliflozin was used as monotherapy, and in 8 studies Dapagliflozin was used as add-on to background antidiabetic therapy or as combination therapy with Metformin Hydrochloride. These data reflect exposure of 2338 patients to Dapagliflozin with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), Dapagliflozin 5 mg (N=1145), or Dapagliflozin 10 mg (N=1131) once daily. The mean age of the population was 55 years and 2% were older than 75 years of age. Fifty percent (50%) of the population were male; 81% were White, 14% were Asian, and 3% were Black or African American. At baseline, the population had Diabetes for an average of 6 years, had a mean hemoglobin A_{1c} (HbA_{1c}) of 8.3%, and 21% had established microvascular complications of Diabetes. Baseline renal function was normal or mildly impaired in 92% of patients and moderately impaired in 8% of patients (mean eGFR 86 mL/min/1.73 m²).
Table 2 shows common adverse reactions associated with the use of Dapagliflozin. These adverse reactions were not present at baseline, occurred more commonly on Dapagliflozin than on placebo, and occurred in at least 2% of patients treated with either Dapagliflozin 5 mg or Dapagliflozin 10 mg.

Adverse Reaction	% of Patients		
	Placebo N=1393	Dapagliflozin 5 mg N=1145	Dapagliflozin 10 mg N=1193
Female genital mycotic infections	1.5	8.4	6.9
Nasopharyngitis	6.2	6.6	6.3
Urinary tract infections [†]	3.7	5.7	4.3
Back pain	3.2	3.1	4.2
Increased urination [‡]	1.7	2.9	3.8
Male genital mycotic infections [§]	0.3	2.8	2.7
Nausea	2.4	2.8	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfort with urination	0.7	1.6	2.1
Pain in extremity	1.4	2.0	1.7

Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulvul abscess, and vaginitis bacterial. (N for females: Placebo=671, Dapagliflozin 5 mg=581, Dapagliflozin 10 mg=598).

Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia urinary tract infection*, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

‡ Increased urination includes the following adverse reactions, listed in order of frequency reported: polyakuria, polyuria, and urine output increased.

§ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, posthitis. (N for males: Placebo=716, Dapagliflozin 5 mg=564, Dapagliflozin 10 mg=595).

Pool of 13 Placebo-Controlled Studies for Dapagliflozin 10 mg

Dapagliflozin 10 mg was also evaluated in a larger placebo-controlled study pool in patients with type 2 diabetes mellitus. This pool combined 13 placebo-controlled studies, including 3 additional studies. 9 add-on to background antidiabetic therapy studies, and an initial combination with metformin study. Across these 13 studies, 2380 patients were treated once daily with Dapagliflozin 10 mg for a mean duration of exposure of 22 weeks. The mean age of the population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the population were male; 84% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 9 years, had a mean HbA1c of 8.2%, and 30% had established microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 m²).

Volume Depletion

Dapagliflozin causes an osmotic diuresis, which may lead to a reduction in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) in patients with type 2 diabetes mellitus for the 12-study and 13-study, short-term, placebo-controlled pools and for the DECLARE study are shown in Table 3.

	Pool of 12 Placebo-Controlled studies			Pool of 13 Placebo-Controlled Studies			DECLARE Study
	Placebo	Dapagliflozin 5 mg	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg
Overall population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)	N=8569 207 (2.4%)	N=8574 213 (2.5%)
Patient Subgroup n (%)							
Patients on loop diuretics	n=55 1 (1.8%)	n=40 0	n=31 3 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)	n=934 57 (6.1%)	n=866 57 (6.6%)
Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/1.73m ²	n=107 2 (1.9%)	n=107 1 (0.9%)	n=89 1 (1.1%)	n=268 1 (1.5%)	n=265 3 (1.9%)	n=658 30 (4.6%)	n=504 2 (5.8%)
Patients ≥65 years of age	n=276 1 (0.4%)	n=216 1 (0.5%)	n=204 3 (1.5%)	n=711 6 (0.8%)	n=665 11 (1.7%)	n=3950 121 (3.1%)	n=3948 117 (3.0%)

* Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

Hypoglycemia

The frequency of hypoglycemia by study in patients with type 2 diabetes mellitus is shown in Table 4. Hypoglycemia was more frequent when Dapagliflozin was added to sulfonylurea or insulin.

	Placebo/Active Control	Dapagliflozin 5 mg	Dapagliflozin 10 mg
Monotherapy (24 weeks)	N=75	N=64	N=70
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	0	0
Add-on to Metformin (24 weeks)	N=137	N=137	N=135
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	0	0
Add-on to Glimepiride (24 weeks)	N=146	N=145	N=151
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	1 (0.7)	3 (2.1)	5 (3.3)
Add-on to Metformin and a Sulfonylurea (24 Weeks)	N=109	-	N=109
Severe [n (%)]	0	-	0
Glucose <54 mg/dL [n (%)]	3 (2.8)	-	7 (6.4)
Add-on to Pioglitazone (24 weeks)	N=139	N=141	N=140
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	1 (0.7)	0
Add-on to DPP4 inhibitor (24 weeks)	N=226	-	N=225
Severe [n (%)]	0	-	1 (0.4)
Glucose <54 mg/dL [n (%)]	1 (0.4)	-	1 (0.4)
Add-on to insulin with or without other OADs (24 weeks)	N=197	N=212	N=196
Severe [n (%)]	1 (0.5)	2 (0.9)	2 (1.0)
Glucose <54 mg/dL [n (%)]	43 (21.8)	55 (25.9)	45 (23.0)

Table 7: Incidence and Rate of Hypoglycemia in Placebo-Controlled Clinical Studies when Sitagliptin was used as Add-On Therapy to Glimepiride (with or without Metformin) or Insulin (with or without Metformin). Regardless of Investigator Assessment of Causality

Add-On to Glimepiride (+/- Metformin) (24 weeks)	Sitagliptin 100 mg + Glimepiride (+/- Metformin)		Placebo + Glimepiride (+/- Metformin)	
	N = 222		N = 219	
Overall (%)	27 (12.2)		4 (1.8)	
Rate (episodes/patient-year) ¹	0.59		0.24	
Severe (%) ²	0 (0.0)		0 (0.0)	
Add-On to Insulin (+/- Metformin) (24 weeks)	Sitagliptin 100 mg + Insulin (+/- Metformin)		Placebo + Insulin (+/- Metformin)	
	N = 322		N = 319	
Overall (%)	50 (15.5)		25 (7.8)	
Rate (episodes/patient-year) ¹	1.06		0.51	
Severe (%) ²	2 (0.6)		1 (0.3)	

¹Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required; intent-to-treat population.
²Based on total number of events (i.e., a single patient may have had multiple events).
³Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.
In a pooled analysis of the two monotherapy studies, the add-on to Metformin study, and the add-on to Pioglitazone study, the overall incidence of adverse reactions of hypoglycemia was 1.2% in patients treated with Sitagliptin 100 mg and 0.9% in patients treated with placebo. In the study of Sitagliptin as add-on combination therapy with Metformin and Rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on Sitagliptin and 0.0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on Sitagliptin and 1.0% in patients given add-on placebo.
In the 24-week, placebo-controlled factorial study of initial therapy with Sitagliptin in combination with Metformin, the incidence of hypoglycemia was 0.6% in patients given placebo, 0.6% in patients given Sitagliptin alone, 0.8% in patients given Metformin alone, and 1.6% in patients given Sitagliptin in combination with Metformin.
In the study of Sitagliptin as initial therapy with Pioglitazone, one patient taking Sitagliptin experienced a severe episode of hypoglycemia. There were no severe hypoglycemia episodes reported in other studies except in the study involving co-administration with insulin.
In an additional, 30-week placebo-controlled, study of patients with type 2 diabetes inadequately controlled with metformin comparing the maintenance of sitagliptin 100 mg versus withdrawal of sitagliptin when initiating basal insulin therapy, the event rate and incidence of documented symptomatic hypoglycemia (blood glucose measurement $\leq$ 70 mg/dL) did not differ between the sitagliptin and placebo groups.

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 (SE) increases in serum creatinine were observed in patients treated with Sitagliptin [0.12 mg/dL (0.04)] and in patients treated with placebo [0.07 mg/dL (0.07)]. The clinical significance of this added increase in serum creatinine relative to placebo is not known.

Postmarketing Experience
Additional adverse reactions have been identified during postapproval use of Sitagliptin as monotherapy and/or in combination with other antihyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis; worsening renal function, including acute renal failure (sometimes requiring dialysis), and tubulointerstitial nephritis; severe and disabling arthralgia; bullous pemphigoid; constipation; vomiting; headache; myalgia, pain in extremity; back pain; pruritus; mouth ulceration; stomatitis; rhabdomyolysis.

4.9. Overdose
Dapagliflozin
There were no reports of overdose during the clinical development program for Dapagliflozin. In the event of an overdose, contact the Poison Control Center. 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
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 indicated 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

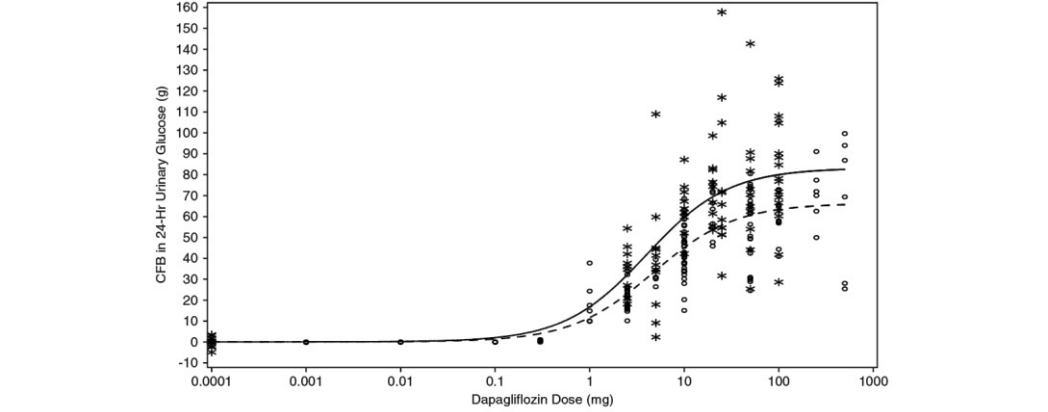
5.1. Mechanism of Action
Dapagliflozin
Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and thereby promotes 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, and decreased intraglomerular pressure which is believed to be mediated by increased tubuloglomerular feedback.

Sitagliptin
Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by Sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity *in vitro* at concentrations approximating those from therapeutic doses.

5.2. Pharmacodynamic properties
Pharmacodynamic Properties
Dapagliflozin

General
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 (see Figure 1). Dapagliflozin dose of 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.

Figure 1: Scatter Plot and Fitted Line of Change from Baseline in 24-Hour Urinary Glucose Amount versus Dapagliflozin Dose in Healthy Subjects and Subjects with Type 2 Diabetes Mellitus (T2DM) (Semi-Log Plot)



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

General
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.

Sitagliptin and Metformin hydrochloride Co-administration
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. Coadministration of sitagliptin and Metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not Metformin, increased active GIP concentrations. It is unclear what these findings mean for changes in glycemic control in patients with type 2 diabetes mellitus.

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 mellitus 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.

5.3. Pharmacokinetic properties

Dapagliflozin
Absorption
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.

Distribution
Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metabolism
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 [¹⁴C]-Dapagliflozin dose and is the predominant drug-related component in human plasma.

Elimination
Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [¹⁴C]-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.

Specific Populations

Renal Impairment
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 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 and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than patients with Type 2 Diabetes with normal renal function. The impact of hemodialysis on Dapagliflozin exposure is not known.

Hepatic Impairment
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.

Effects of Age, Gender, Race, and Body Weight on Pharmacokinetics
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.

Pediatric
Pharmacokinetics in the pediatric population has not been studied.

Drug Interactions

In Vitro Assessment of Drug Interactions
In *in vitro* studies, Dapagliflozin and Dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, or 3A4, nor induced CYP 1A2, 2B6, or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter, and Dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or Dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, Dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

Effects of Other Drugs on Dapagliflozin
Table 8 shows the effect of coadministered drugs on the pharmacokinetics of Dapagliflozin. No dose adjustments are recommended for Dapagliflozin.

Coadministered Drug (Dose Regimen) *	Dapagliflozin (Dose Regimen)	Effect on Dapagliflozin Exposure (% Change [90% CI])	
No dosing adjustments required for the following:		---	AUC [†]
Oral Antidiabetic Agents			
Metformin Hydrochloride (1000 mg)	20 mg	↔	↔
Pioglitazone (45 mg)	50 mg	↔	↔
Sitagliptin (100 mg)	20 mg	↔	↔
Glimepiride (4 mg)	20 mg	↔	↔
Voglibose (0.2 mg three times daily)	10 mg	↔	↔
Other Medications			
Hydrochlorothiazide (25 mg)	50 mg	↔	↔
Bumetanide (1 mg)	10 mg once daily for 7 days	↔	↔
Valsartan (320 mg)	20 mg	↓12% [↓3%, ↓20%]	↔
Simvastatin (40 mg)	20 mg	↔	↔
Anti-infective Agent			
Rifampin (600 mg once daily for 6 days)	10 mg	↓7% [↓22%, ↑11%]	↓22% [↓27%, 17%]
Nonsteroidal Anti-inflammatory Agent			
Mefenamic Acid (loading dose of 500 mg followed by 14 doses of 250 mg every 6 hours)	10 mg	↑13% [↑3%, ↑24%]	↑51% [↑44%, 58%]

* Single dose unless otherwise noted.
[†]AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.
↔ = no change (geometric mean ratio of test: reference within 0.80 to 1.25); ↓ or ↑ = parameter was lower or higher, respectively, with coadministration compared to Dapagliflozin administered alone (geometric mean ratio of test: reference was lower than 0.80 or higher than 1.25).

Effects of Dapagliflozin on Other Drugs
Table 9 shows the effect of Dapagliflozin on other co-administered drugs. Dapagliflozin did not meaningfully affect the pharmacokinetics of the co-administered drugs.

Table 9: Effects of Dapagliflozin on the Systemic Exposures of Co-administered Drugs			
Co-administered Drug (Dose Regimen)	Dapagliflozin (Dose Regimen)	Effects on Co-administered Drug Exposure (% Change [90% CI])	
		C _{max}	AUC [†]
No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin Hydrochloride (1000 mg)	20 mg	↔	↔
Pioglitazone (45 mg)	50 mg	↓7% [↓25%, ↑15%]	↔
Sitagliptin (100 mg)	20 mg	↔	↔
Glimepiride (4 mg)	20 mg		↑13% [0%, ↑29%]
Other Medications			
Hydrochlorothiazide (25 mg)	50 mg	↔	↔
Bumetanide (1 mg)	10mg once daily for 7 days	↑13% [↓2%, ↑31%]	↑13% [↓1%, ↑30%]
Valsartan (320 mg)	20 mg	↓6% [↓24%, ↑16%]	↓5% [↓15%, ↑29%]
Simvastatin (40 mg)	20 mg	↔	↑19%
Digoxin (0.25 mg)	20 mg loading dose then 10 mg once daily for 7 days	↔	↔
Warfarin (25mg)	20 mg loading dose then 10 mg once daily for 7 days	↔	↔

* Single dose unless otherwise noted.
[†]AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.
↔ = no change (geometric mean ratio of test: reference within 0.80 to 1.25); ↓ or ↑ = parameter was lower or higher, respectively, with coadministration compared to Dapagliflozin administered alone (geometric mean ratio of test: reference was lower than 0.80 or higher than 1.25).

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

Absorption
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%.

Effect of Food
Coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.

Distribution
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%).

Elimination
Approximately 75% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. The apparent terminal t_{1/2} following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

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

Excretion
Following administration of an oral [¹⁴C] Sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing.

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

Special Populations
Patients with Renal Impairment
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.

Patients with Hepatic Impairment
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. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score >9).

Effects of Age, Body Mass Index (BMI), Gender, and Race
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.

Drug Interaction Studies
In Vitro Assessment of Drug Interactions
Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a P-gp substrate but does not inhibit P-gp mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways. Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

In Vivo Assessment of Drug Interactions
Effect of Sitagliptin on Other Drugs
In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of Metformin, glyburide, simvastatin, rosiglitazone, digoxin, warfarin, or an oral contraception (ethinyl estradiol and norethindrone), providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, P-gp, and organic cationic transporter (OCT).

Table 10: Effect of Sitagliptin on Systemic Exposure of Coadministered Drugs				
Coadministered Drug	Dose of Coadministered Drug	Dose of Sitagliptin ^a	Geometric Mean Ratio (ratio with/without sitagliptin) No Effect = 1.00	
			AUC ^b	C _{max}
Digoxin	0.25 mg ^c once daily for 10 days	100 mg ^c once daily for 10 days	Digoxin 1.11 ^d	1.18
Glyburide	1.25 mg	200 mg ^c once daily for 6 days	Glyburide 1.09	1.01
Simvastatin	20 mg	200 mg ^c once daily for 5 days	Simvastatin 0.85 ^e	0.80
			Simvastatin Acid 1.12 ^f	1.06
Rosiglitazone	4 mg	200 mg ^c once daily for 5 days	Rosiglitazone 0.98	0.99
Warfarin	30 mg single dose on day 5	200 mg ^c once daily for 11 days	S (-) Warfarin 0.95	0.89
			R (+) Warfarin 0.99	0.89
Ethinyl estradiol and norethindrone	21 days once daily of 35 µg ethinyl estradiol with norethindrone 0.5 mg x 7 days, 0.75 mg x 7 days, 1.0 mg x 7 days	200 mg ^c once daily for 21 days	Ethinyl estradiol 0.99	0.97
			Norethindrone 1.03	0.98
Metformin HCl	1000 mg ^c twice daily for 14 days	50 mg ^c twice daily for 7 days	Metformin 1.02 ^g	0.97

^aAll doses administered as single dose unless otherwise specified.
^bAUC is reported as AUC_{0-∞} unless otherwise specified.
^cMultiple dose.
^dAUC_{0-24hr}}
^eAUC_{0-6hr}}
^fAUC_{0-12hr}}
Effects of Other Drugs on Sitagliptin
Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by co-administered medications (Table 11).

Table 11: Effect of Co-administered Drugs on Systemic Exposure of Sitagliptin				
Co-administered Drug	Dose of Co-administered Drug ^a	Dose of Sitagliptin ^a	Geometric Mean Ratio (Ratio with/ without Co-administered drug) No Effect = 1.00	
			AUC ^b	C _{max}
Cyclosporine	600 mg once daily	100 mg once daily	Sitagliptin 1.29	1.68
Metformin HCl	1000 mg ^c twice daily for 14 days	50 mg ^c twice daily for 7 days	Sitagliptin 1.02 ^d	1.05

All doses administered as single dose unless otherwise specified.
^aAUC is reported as AUC_{0-∞} unless otherwise specified.
^bMultiple doses.
^cAUC_{0-24hr}}

6. NONCLINICAL PROPERTIES

6.1. Animal Toxicology or Pharmacology
Dapagliflozin
Carcinogenesis, Mutagenesis, Impairment of Fertility
Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were approximately 72 times (males) and 105 times (females) the clinical dose of 10 mg per day based on AUC exposure. In rats, the highest dose was approximately 131 times (males) and 186 times (females) the clinical dose of 10 mg per day based on AUC exposure.
Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of *in vitro* clastogenicity assays in the presence of S9 activation and at concentrations $\geq$ 100 µg/mL. Dapagliflozin was negative for clastogenicity in a series of *in vivo* studies evaluating micronuclei or DNA repair in rats at exposure multiples $\geq$ 2100 times the clinical dose. There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.
Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples $\leq$ 1708 times and 998 times the maximum recommended human dose in males and females, respectively.

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 tumors were not observed at 150 mg/kg, approximately 20 times the human exposure at the MRHD. A two-year carcinogenicity study was conducted in male and female mice given oral doses of Sitagliptin of 50, 125, 250, and 500 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 500 mg/kg, approximately 70 times human exposure at the MRHD. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an *in vitro* cytogenetics assay in CHO, an *in vitro* rat hepatocyte DNA alkaline elution assay, and an *in vivo* micronucleus assay.
In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination (approximately 8 weeks total) and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, nondose-related increased resorptions