**For the use of a registered medical practitioner or a hospital or a laboratory only**

# Rx Dapagliflozin & Sitagliptin Tablets

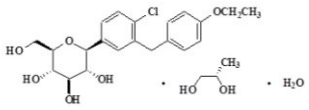
## DAPAONE-S®

**Composition:**
Each film coated tablet contains:
Dapagliflozin Propanediol USP
eq. to Dapagliflozin 5 mg
Sitagliptin Phosphate Monohydrate IP
eq. to Sitagliptin 50 mg
Excipients q.s.
Colour: Titanium Dioxide IP

**Composition:**
Each film coated tablet contains:
Dapagliflozin Propanediol USP
eq. to Dapagliflozin 10 mg
Sitagliptin Phosphate Monohydrate IP
eq. to Sitagliptin 100 mg
Excipients q.s.
Colour: Titanium Dioxide IP

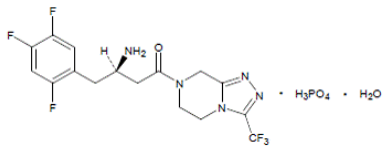
DOSAGE FORM
Tablet

DESCRIPTION
Dapagliflozin
Chemical Formula: C21H25ClO6•C3H8O2•H2O
Molecular Weight: 502.98 g/mol
Therapeutic Categories: sodium-glucose co-transporter 2 (SGLT2) inhibitor.
Chemical Name: D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4¬ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate.



Sitagliptin

Chemical Formula: C16H15F6N5OH3PO4H2O
Molecular Weight: Average: 523.32 g/mol
Therapeutic Categories: oral antihyperglycemic
ChemicalName: 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8¬tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate.



INDICATION
As adjunct to diet and exercise to improve glycemic control in adults with type-II diabetes
DOSAGE AND ADMINISTRATION
Dosage: Twice a day or as directed by registered medical practitioner.

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 in pregnancy.
In animal studies, adverse renal pelvic and tubule dilatations, 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 embryo fetal risk
Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, 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 dilatations 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 dilatations 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 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 embryo fetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy. In rats, dapagliflozin was neither embryo lethal 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).
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 dilatations) 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 glycemic control. 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.
Renal Impairment
Use of dapagliflozin is not recommended when eGFR is less than 45 mL/min/1.73 m2 and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m2) or ESRD.
Dapagliflozin was evaluated in two glycemic control studies that included patients 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 60 mL/min/1.73 m2 , respectively). The safety profile of dapagliflozin in the study of patients with an eGFR of 45 to less than 60 mL/min/1.73 m2 was similar to the general population of patients with type 2 diabetes. Although patients in the dapagliflozin arm had reduction in eGFR compared to the placebo arm, eGFR generally returned towards baseline after treatment discontinuation. Patients with renal impairment using dapagliflozin for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury. 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.
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
Pregnancy Category B: 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. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a registry to monitor the pregnancy outcomes of women exposed to SITAGLIPTIN while pregnant. Health care providers are encouraged to report any prenatal exposure. Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30- and 20-times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD. Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats. Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.
Nursing Mothers Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SITAGLIPTIN is administered to a nursing woman.
Pediatric Use Safety and effectiveness of SITAGLIPTIN in pediatric patients under 18 years of age have not been established. 8.5 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. No overall differences in safety or effectiveness were observed 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. This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly, and it may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter

CONTRA-INDICATION
Dapagliflozin Propanediol monohydrate Eq. to Dapagliflozin 5mg /10mg + Sitagliptin phosphate monohydrate IP eq. to sitagliptin 100mg /100mg film contraindicated in patients with:
• History of a serious hypersensitivity reaction to dapagliflozin, such as anaphylactic reactions or angioedema.
• Severe renal impairment, (eGFR less than 30 mL/min/1.73 m2 ) end-stage renal disease (ESRD), or patients on dialysis.

WARNINGS AND PRECAUTIONS DAPAGLIFLOZIN
Hypotension
Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating dapagliflozin particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m2 ), elderly patients, or patients on loop diuretics. Before initiating dapagliflozin in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.
Ketoacidosis
Reports of ketoacidosis, 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. Fatal cases of ketoacidosis 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 ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with dapagliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, dapagliflozin should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis 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 ketoacidosis was not immediately recognized, and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (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 predisposing to ketoacidosis, 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 ketoacidosis, 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 ketoacidosis and temporarily discontinuing dapagliflozin in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting dapagliflozin.
Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue dapagliflozin and seek medical attention immediately if signs and symptoms occur.
Acute Kidney Injury
Dapagliflozin causes intravascular volume contraction, and can cause acute kidney injury. There have been post marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving dapagliflozin.

Increases in serum creatinine and decreases in estimated GFR may also be observed with initiation of dapagliflozin. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Before initiating dapagliflozin, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing dapagliflozin in the setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue dapagliflozin promptly and institute treatment.
Renal function should be evaluated prior to initiation of dapagliflozin and monitored periodically thereafter. Use of dapagliflozin is not recommended when the eGFR is less than 45 mL/min/1.73 m2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2.
Urosepsis and Pyelonephritis
There have been post marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization 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.
Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in post marketing surveillance 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 glycemic 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.

Sitagliptin
Pancreatitis There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic 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.

Renal Impairment 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 insufficiency and in patients with ESRD requiring hemodialysis or peritoneal dialysis. [See Dosage and Administration (2.2); Clinical Pharmacology (12.3).] Caution should be used to ensure that the correct dose of SITAGLIPTIN is prescribed for patients with moderate.

Use with Medications Known to Cause Hypoglycemia 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. [See Adverse Reactions (6.1).] Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

Hypersensitivity Reactions There have been postmarketing 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.

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

ADVERSE REACTIONS
The most common adverse reactions associated with dapagliflozin (5% or greater incidence) were female genital mycotic infections, nasopharyngitis, and urinary tract infections.
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 practice. In controlled clinical studies as both monotherapy and combination therapy with metformin, pioglitazone, or rosiglitazone and metformin, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to clinical adverse reactions with SITAGLIPTIN were similar to placebo. In combination with glimepiride, with or without metformin, the overall incidence of clinical adverse reactions with SITAGLIPTIN was higher than with placebo, in part related to a higher incidence of hypoglycemia the incidence of discontinuation due to clinical adverse reactions was similar to placebo.

OVERDOSAGE 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
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 [see Clinical Pharmacology (12.2)]. 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.

CLINICAL PHARMACOLOGY DAPAGLIFLOZIN
Mechanism of Action 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.
Pharmacodynamics 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. 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.
Pharmacokinetics Absorption
Following oral administration of dapagliflozin, the maximum plasma concentration (Cmax) is usually attained within 2 hours under fasting state. The Cmax 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 Cmax by up to 50% and prolongs Tmax 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 (t½) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

SITAGLIPTIN
Mechanism of Action
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.

Pharmacodynamics 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 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 how these findings relate to changes in glycemic control in patients with type 2 diabetes. 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 was observed at 3 hours postdose and was 8,0 msec. This increase is not considered to be clinically significant. At the 800 mg dose, peak sitagliptinplasma 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.

Pharmacokinetics The pharmacokinetics of sitagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours postdose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100 mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 □M•hr, Cmax was 950 nM, and apparent terminal half- life (t1/2) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes. Absorption The absolute bioavailability of sitagliptin is approximately 87%. Because coadministration of a high-fat meal with SITAGLIPTIN had no effect on the pharmacokinetics, SITAGLIPTIN may be administered with or without food. Distribution 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 Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. 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. The apparent terminal t1/2 following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Special Populations Renal Insufficiency A single-dose, open-label study was conducted to evaluate the pharmacokinetics of SITAGLIPTIN (50 mg dose) in patients with varying degrees of chronic renal insufficiency compared to normal healthy control subjects. The study included patients with renal
insufficiency classified on the basis of creatinine clearance as mild (50 toCompared to normal healthy control subjects, an approximate 1.1- to 1.6-fold increase in plasma AUC of sitagliptin was observed in patients with mild renal insufficiency. Because increases of this magnitude are not clinically relevant, dosage adjustment in patients with mild renal insufficiency is not necessary. Plasma AUC levels of sitagliptin were increased approximately 2-fold and 4-fold in patients with moderate renal insufficiency and in patients with severe renal insufficiency, including patients with ESRD on hemodialysis, respectively. Sitagliptin was modestly removed by hemodialysis (13.5% over a 3- to 4-hour hemodialysis session starting 4 hours postdose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal insufficiency, as well as in ESRD patients requiring hemodialysis. [See Dosage and Administration (2.2).] Hepatic Insufficiency In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and Cmax of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100 mg dose of SITAGLIPTIN. These differences are not considered to be clinically meaningful. No dosage adjustment for SITAGLIPTIN is necessary for patients with mild or moderate hepatic insufficiency. There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9). Body Mass Index (BMI) No dosage adjustment is necessary based on BMI. Body mass index had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data. Gender No dosage adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data. Geriatric No dosage adjustment is required based solely on age. 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 Studies characterizing the pharmacokinetics of sitagliptin in pediatric patients have not been performed. Race No dosage adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of available pharmacokinetic data, including subjects of white, Hispanic, black, Asian, and other racial groups. Drug Interactions In Vitro Assessment of Drug Interactions Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a p- glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways. Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low. In Vivo Assessment of Drug Interactions Effects of Sitagliptin on Other Drugs In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing in vivo evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of SITAGLIPTIN daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma Cmax by 18%.

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

INCOMPATIBILITIES
No incompatibility study has been found

PACKAGING INFORMATION
10 tablets packed in an Alu-Alu blister.
2 tablets packed in an Alu-Alu blister.

SHELF LIFE:
Refer on carton.

**Storage: Store protected from light & moisture, at a temperature not exceeding 30°C.**

Keep the medicine out of reach of children.

Mfg. Lic. No.: 68/UA/2009
Mfg License valid up to 21.11.2024

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