SITAGLIP®

सिटाग्लिप

(Sitagliptin)

SITAGLIP is a once-daily prescription pill that, along with diet and exercise, helps lower blood sugar levels in adults with type-II diabetes.

CLINICAL PHARMACOLOGY:

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 SITAGLIP, 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, SITAGLIP 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 SITAGLIP 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. ***Co-administration of Sitagliptin and Metformin had an additive effect on active GLP-1 concentrations.*** Sitagliptin, but not Metformin, increases 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. 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.

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. Plasma AUC of Sitagliptin increased approximately 14% following 100 mg doses at steady-state compared to the first dose.

Absorption:

The absolute bioavailability of Sitagliptin is approximately 87%. Because co-administration of a high-fat meal with SITAGLIP had no effect on the pharmacokinetics, SITAGLIP 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 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 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.

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 SITAGLIP 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.

Gender:

No dosage adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of Sitagliptin.

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.

INDICATIONS AND USAGE:

Monotherapy and Combination Therapy:

SITAGLIP is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Limitations:

SITAGLIP should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

Sitagliptin has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin.

DOSAGE AND ADMINISTRATION:

Recommended Dosing:

The recommended dose of SITAGLIP is 100 mg once daily. SITAGLIP can be taken with or without food.

Patients with Renal Insufficiency:

For patients with mild renal insufficiency (creatinine clearance [CrCl] greater than or equal to 50 mL/min, approximately corresponding to serum creatinine levels of less than or equal to 1.7 mg/dL in men and less than or equal to 1.5 mg/dL in women), no dosage adjustment for SITAGLIP is required.

For patients with moderate renal insufficiency (CrCl greater than or equal to 30 to less than 50 mL/min, approximately corresponding to serum creatinine levels of greater than 1.7 to less than or equal to 3.0 mg/dL in men and greater than 1.5 to less than or equal to 2.5 mg/dL in women), the dose of SITAGLIP is 50 mg once daily.

For patients with severe renal insufficiency (CrCl less than 30 mL/min, approximately corresponding to serum creatinine levels of greater than 3.0 mg/dL in men and greater than 2.5 mg/dL in women) or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dose of SITAGLIP is 25 mg once daily. SITAGLIP may be administered without regard to the timing of dialysis. Because there is a need for dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of SITAGLIP and periodically thereafter. There have been post-marketing reports of worsening renal function in patients with renal insufficiency, some of whom were prescribed inappropriate doses of Sitagliptin.

Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin:

When SITAGLIP is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia.

CONTRAINDICATIONS:

Sitagliptin is contraindicated if history of a serious hypersensitivity reaction to Sitagliptin, such as anaphylaxis or angioedema is there.

WARNINGS AND PRECAUTIONS:

Pancreatitis:

After initiation of SITAGLIP, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, SITAGLIP 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 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of SITAGLIP 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. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of SITAGLIP.

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. 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. If a hypersensitivity reaction is suspected, discontinue SITAGLIP, 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.

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 4 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. If bullous Pemphigoid is suspected, SITAGLIP should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

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, Sitagliptin did not meaningfully alter the pharmacokinetics of Metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing in vivo evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT).

Digoxin:

Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of Sitagliptin daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma Cmax by 18%.

Metformin:

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

Sulfonylureas:

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

Simvastatin:

Single-dose pharmacokinetics of simvastatin, a CYP3A4 substrate, was not meaningfully altered in subjects receiving multiple daily doses of Sitagliptin. Therefore, Sitagliptin is not an inhibitor of CYP3A4-mediated metabolism.

Thiazolidinediones:

Single-dose pharmacokinetics of rosiglitazone was not meaningfully altered in subjects receiving multiple daily doses of Sitagliptin, indicating that SITAGLIP is not an inhibitor of CYP2C8-mediated metabolism.

Warfarin:

Multiple daily doses of Sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Because S(-) warfarin is primarily metabolized by CYP2C9, these data also support the conclusion that Sitagliptin is not a CYP2C9 inhibitor.

Oral Contraceptives:

Co-administration with Sitagliptin did not meaningfully alter the steady-state pharmacokinetics of norethindrone or ethinyl estradiol. Effects of Other Drugs on Sitagliptin Clinical data described below suggest that Sitagliptin is not susceptible to clinically meaningful interactions by co-administered medications.

Cyclosporine:

A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of Sitagliptin. Co-administration of a single 100 mg oral dose of Sitagliptin and a single 600 mg oral dose of cyclosporine increased the AUC and Cmax of Sitagliptin by approximately 29% and 68%, respectively. These modest changes in Sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of Sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

USE IN SPECIFIC POPULATIONS:

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.

Nursing Mothers:

Sitagliptin is secreted in the milk of lactating rats at 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 SITAGLIP is administered to a nursing woman.

Pediatric Use:

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

Geriatric Use:

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.

OVERDOSAGE:

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.

DOSAGE FORMS & STRENGTHS:

SITAGLIP tablets are available as:

- 50 mg FCT (Film Coated Tablets)
  Packaging: 10 Tablets X 10 Blisters
- 100 mg FCT (Film Coated Tablets)
  Packaging: 10 Tablets X 10 Blisters

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