JENTIN MET XR
(Sitagliptin + Metformin HCl)

50mg+500mg, 50mg+1000mg & 100mg+1000mg

Tablets

WARNING

Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. • Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. • If acidosis is suspected, discontinue Jentin Met XR and hospitalize the patient immediately.

COMPOSITION

Jentin Met XR 50mg+500mg tablets
Each film-coated tablet contains:
Sitagliptin Phosphate Monohydrate equivalent to Sitagliptin ….50mg
(as Immediate Release Coating)
Metformin Hydrochloride……...500mg
(as Extended Release Core)
(As per Innovator's Specifications)

Jentin Met XR 50mg+1000mg tablets
Each film-coated tablet contains:
Sitagliptin Phosphate Monohydrate equivalent to Sitagliptin ….50mg
(as Immediate Release Coating)
Metformin Hydrochloride …. 1000mg
(as Extended Release Core)
(As per Innovator's Specifications)

Jentin Met XR 100mg+1000mg tablets
Each film-coated tablet contains:
Sitagliptin Phosphate Monohydrate equivalent to Sitagliptin ….100mg
(as Immediate Release Coating)
Metformin Hydrochloride …. 1000mg
(as Extended Release Core)
(As per Innovator's Specifications)

THERAPEUTIC INDICATIONS

For adult patients

Sitagliptin + Metformin HCl XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

Sitagliptin + Metformin HCl XR should not be used in patients with type 1 diabetes mellitus. Sitagliptin + Metformin HCl XR 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 + Metformin HCL.

DOSAGE AND ADMINISTRATION

Recommended Dosing

• Take Sitagliptin + Metformin HCl XR orally once daily with a meal. Patients taking two Sitagliptin + Metformin HCl XR tablets should take the two tablets together once daily.
• Individualize the dosage of Sitagliptin + Metformin HCl XR on the basis of the patient's current regimen, effectiveness, and tolerability.
• The maximum recommended daily dose is 100 mg of sitagliptin and 2000 mg of metformin hydrochloride (HCl) extended-release.
• The recommended starting dose in patients not currently treated with metformin is 100 mg sitagliptin and 1000 mg metformin HCl extended-release once daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin.
• The starting dose in patients already treated with metformin should provide 100 mg sitagliptin and the previously prescribed dose of metformin.
• For patients taking metformin HCl immediate-release 850 mg twice daily or 1000 mg twice daily, the recommended starting dose of Sitagliptin + Metformin HCl XR is two 50 mg sitagliptin and 1000 mg metformin HCl extended-release tablets taken together once daily.
• Maintain the same total daily dose of sitagliptin and metformin when changing between Jentin Met (sitagliptin and metformin HCl immediate-release) and Jentin Met XR.
• Do not split, crush or chew Sitagliptin + Metformin HCl XR tablets.

Special populations

Renal Impairment
- Assess renal function prior to initiation of Sitagliptin + Metformin HCl XR and periodically thereafter.
- Sitagliptin + Metformin HCl XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2. Discontinue Sitagliptin + Metformin HCl XR if the patient's eGFR later falls below 30 mL/min/1.73 m^2
- Initiation of Sitagliptin + Metformin HCl XR in patients with an eGFR between 30 and 45 mL/min/1.73 m^2 is not recommended.
- In patients taking Sitagliptin + Metformin HCl XR whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy and limit dose of the sitagliptin component to 50 mg once daily.

Hepatic impairment
Sitagliptin + Metformin HCl XR must not be used in patients with hepatic impairment. Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis.

Elderly
As metformin and sitagliptin are excreted by the kidney, Sitagliptin + Metformin HCl XR should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly.

Pediatric population
Sitagliptin + Metformin HCl XR should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Sitagliptin + Metformin HCl XR has not been studied in pediatric patients under 10 years of age.

Discontinuation for Iodinated Contrast Imaging Procedures
Discontinue Sitagliptin + Metformin HCl XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Reevaluate eGFR 48 hours after the imaging procedure; restart Sitagliptin + Metformin HCl XR if renal function is stable.

CONTRAINDICATIONS

Sitagliptin + Metformin HCl XR is contraindicated in patients with:
- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2)
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis.
- History of a serious hypersensitivity reaction to Sitagliptin + Metformin HCL, sitagliptin, or metformin such as anaphylaxis or angioedema.

WARNINGS AND PRECAUTIONS

Lactic Acidosis
There have been post marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate/pyruvate ratio; metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk. Educate patients and their families about the symptoms of lactic acidosis
If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Sitagliptin + Metformin HCL. Hemodialysis has often resulted in reversal of symptoms and recovery.
For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:
Renal Impairment: The post marketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment because metformin is substantially excreted by the kidney. Obtain an eGFR at least annually in all patients taking Sitagliptin + Metformin HCL. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently
Drug Interactions**:** The concomitant use of Sitagliptin + Metformin HCl XR with specific drugs may increase the risk of metformin associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation. Therefore, consider more frequent monitoring of patients.
Age 65 or Greater**:** The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients

Radiological Studies with Contrast**:** Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Re-evaluate eGFR 48 hours after the imaging procedure, and restart Sitagliptin + Metformin HCl XR if renal function is stable**.**

Surgery and Other Procedures**:** Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Sitagliptin + Metformin HCl XR should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States**:** Several of the post marketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Sitagliptin + Metformin HCL.

Excessive Alcohol Intake**:** Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving Sitagliptin + Metformin HCl XR

Hepatic Impairment**:** Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of Sitagliptin + Metformin HCl XR in patients with clinical or laboratory evidence of hepatic disease.

Pancreatitis

There have been post marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin with or without metformin. After initiation of Sitagliptin + Metformin HCL, patients should be observed carefully for signs and symptoms of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin + Metformin HCl XR

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 Sitagliptin + Metformin HCl XR 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 + Metformin HCl XR

Acute Renal Failure

There have been post marketing reports of worsening renal function in patients taking sitagliptin with or without metformin, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with Sitagliptin + Metformin HCl XR and at least annually thereafter, renal function should be assessed. Sitagliptin + Metformin HCl XR is contraindicated in patients with severe renal impairment

Vitamin B12 Deficiency

Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 measurements at 2- to 3-year intervals in patients on Sitagliptin + Metformin HCl XR and manage any abnormalities

Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues

Sitagliptin + Metformin HCl XR may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue (e.g., sulfonylurea). A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with Sitagliptin + Metformin HCL.

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. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the 7 first dose. If a hypersensitivity reaction is suspected, discontinue Sitagliptin + Metformin HCL, assess for other potential causes for the event, and institute alternative treatment for diabetes. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Sitagliptin + Metformin HCL.

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 + Metformin HCL. If bullous pemphigoid is suspected, Sitagliptin + Metformin HCl XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

DRUG INTERACTIONS

Carbonic Anhydrase Inhibitors: examples include Topiramate, zonisamide, acetazolamide or dichlorphenamide.	
Clinical Impact:	Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Sitagliptin + Metformin HCl XR may increase the risk for lactic acidosis.
Intervention:	Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance: examples include Ranolazine, vandetanib, dolutegravir, and cimetidine.	
Clinical Impact:	Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin could increase systemic exposure to metformin and may increase the risk for lactic acidosis
Intervention:	Consider the benefits and risks of concomitant use with Sitagliptin + Metformin HCl XR
Alcohol	
Clinical Impact:	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention:	Warn patients against alcohol intake while receiving Sitagliptin + Metformin HCl XR
Insulin Secretagogues or Insulin	
Clinical Impact:	Coadministration of Sitagliptin + Metformin HCl XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia.
Intervention:	Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.
Drugs Affecting Glycemic Control: examples include Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid.	
Clinical Impact:	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.
Intervention:	When such drugs are administered to a patient receiving Sitagliptin + Metformin HCL, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Sitagliptin + Metformin HCL, observe the patient closely for hypoglycemia.

PREGNANCY

There are no adequate data from the use of sitagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses of sitagliptin.

A limited amount of data suggests the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development.

Sitagliptin + Metformin HCl XR should not be used during pregnancy. If a patient wishes to become pregnant or if a pregnancy occurs, treatment should be discontinued and the patient switched to insulin treatment as soon as possible.

BREAST-FEEDING

No studies in lactating animals have been conducted with the combined active substances of this medicinal product. In studies performed with the individual active substances, both sitagliptin and metformin are excreted in the milk of lactating rats. Metformin is excreted in human milk in small amounts. It is not known whether sitagliptin is excreted in human milk. Sitagliptin + Metformin HCl XR must therefore not be used in women who are breast-feeding.

FERTILITY

Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

ADVERSE REACTIONS

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 practice.
The most common adverse reactions reported in ≥5% of patients simultaneously started on sitagliptin and metformin and more commonly than in patients treated with placebo were Abdominal pain or discomfort, Nausea, Vomiting, Diarrhea, upper respiratory tract infections, nasopharyngitis, peripheral edema, headache and hypoglycemia when used in combination with Insulin or Insulin Secretagogues.

Post marketing Experience

Additional adverse reactions have been identified during post approval use of sitagliptin with metformin, sitagliptin, or metformin. 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; upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis; worsening renal function, including acute renal failure (sometimes requiring dialysis); severe and disabling arthralgia; bullous pemphigoid; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; mouth ulceration; stomatitis; cholestatic, hepatocellular, and mixed hepatocellular liver injury; rhabdomyolysis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com.

OVERDOSAGE

In the event of an overdose, it is reasonable to employ 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.
Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mechanism of Action

SITAGLIPTIN + METFORMIN HCL XR
SITAGLIPTIN + METFORMIN HCL XR tablets combine two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes mellitus: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin extended-release, a member of the biguanide class.
Sitagliptin
Sitagliptin is a DPP-4 inhibitor, which exerts 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.
Metformin
Metformin is a biguanide that improves glycemic control in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

Pharmacodynamics

Sitagliptin
In patients with type 2 diabetes mellitus, 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 Coadministration
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.

Pharmacokinetic properties

SITAGLIPTIN + METFORMIN HCL XR
After administration of two SITAGLIPTIN + METFORMIN HCL XR 50 mg/1000 mg tablets once daily with the evening meal for 7 days in healthy adult subjects, steady-state for sitagliptin and metformin is reached by Day 4 and 5, respectively.
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 μM•hr, Cmax was 950 nM, and apparent terminal half-life (t½) 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
SITAGLIPTIN + METFORMIN HCL XR
After administration of SITAGLIPTIN + METFORMIN HCL XR tablets once daily, the median Tmax value for sitagliptin and metformin at steady state is approximately 3 and 8 hours post dose, respectively. The median Tmax value for sitagliptin and metformin after administration of a single tablet of JANUMET is 3 and 3.5 hours post dose, respectively.
Effect of Food
After administration of SITAGLIPTIN + METFORMIN HCL XR tablets with a high-fat breakfast, the AUC for sitagliptin was not altered. The mean Cmax was decreased by 17%, although the median Tmax was unchanged

relative to the fasted state. After administration of SITAGLIPTIN + METFORMIN HCL XR with a high-fat breakfast, the AUC for metformin increased 62%, the Cmax for metformin decreased by 9%, and the median Tmax for metformin occurred 2 hours later relative to the fasted state.

Sitagliptin

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. 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.

Metformin

The absolute bioavailability of a metformin HCl 500-mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin HCl tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg (approximately 1.3 times the maximum recommended daily dosage), indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Effect of Food

Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850-mg tablet of metformin HCl with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Sitagliptin

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Metformin

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin HCl tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 mcg/mL.

Elimination

Sitagliptin

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. 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.

Metformin

Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metabolism

Sitagliptin

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.

Metformin

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Metabolism studies with extended-release metformin tablets have not been conducted.

Excretion

Sitagliptin

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 (P-gp), which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a P-gp inhibitor, did not reduce the renal clearance of sitagliptin.

Metformin

Elimination of metformin occurs primarily via renal excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

Specific Populations

Patients with Renal Impairment

SITAGLIPTIN + METFORMIN HCL XR

Studies characterizing the pharmacokinetics of sitagliptin and metformin after administration of SITAGLIPTIN + METFORMIN HCL XR in renally impaired patients have not been performed.

Sitagliptin

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

Metformin

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased.

Patients with Hepatic Impairment

SITAGLIPTIN + METFORMIN HCL XR

Studies characterizing the pharmacokinetics of sitagliptin and metformin after administration of SITAGLIPTIN + METFORMIN HCL XR in patients with hepatic impairment have not been performed.

Sitagliptin

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

Metformin

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

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

Sitagliptin

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

Metformin

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

Drug Interaction Studies

SITAGLIPTIN + METFORMIN HCL XR

Coadministration of multiple doses of sitagliptin (50 mg) and metformin HCl (1000 mg) given twice daily did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

Pharmacokinetic drug interaction studies with SITAGLIPTIN + METFORMIN HCL XR have not been performed; however, such studies have been conducted with the individual components of SITAGLIPTIN + METFORMIN HCL XR (sitagliptin and metformin extended-release).

Sitagliptin

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

Effects 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).

Effects of Other Drugs on Sitagliptin

Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by coadministered medications

Metformin

Table: Effect of Metformin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without metformin) No Effect = 1.00		
				AUC †	Cmax
Cimetidine	400 mg	850 mg	Cimetidine	0.95 ‡	1.01
Glyburide	5 mg	500 mg§	Glyburide	0.78 ¶	0.63 ¶
Furosemide	40 mg	850 mg	Furosemide	0.87 ¶	0.69 ¶
Nifedipine	10 mg	850 mg	Nifedipine	1.10 ‡	1.08
Propranolol	40 mg	850 mg	Propranolol	1.01 ‡	0.94
Ibuprofen	400 mg	850 mg	Ibuprofen	0.97 #	1.01 #

* All doses administered as single dose unless otherwise specified
†AUC is reported as AUC0-∞ unless otherwise specified
‡AUC0-24hr
§ metformin HCl extended-release tablets 500 mg
¶Ratio of arithmetic means, p value of difference <0.05
Ratio of arithmetic means

Table: Effect of Coadministered Drugs on Systemic Exposure of Metformin

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC †	Cmax
Glyburide	5 mg	500 mg‡	Metformin‡	0.98 §	0.99 §
Furosemide	40 mg	850 mg	Metformin	1.09 §	1.22 §
Nifedipine	10 mg	850 mg	Metformin	1.16	1.21
Propranolol	40 mg	850 mg	Metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	Metformin	1.05 §	1.07 §
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin.					
Cimetidine	400 mg	850 mg	Metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis					
Topiramate	100 mg¶	500 mg¶	Metformin	1.25 ¶	1.17

*All doses administered as single dose unless otherwise specified
†AUC is reported as AUC0-∞ unless otherwise specified
‡ metformin HCl extended-release tablets 500 mg
§ Ratio of arithmetic means
¶Steady state 100 mg Topiramate every 12 hr + metformin HCl 500 mg every 12 hr. AUC = AUC0-12hr

Summary of Clinical Studies

The coadministration of sitagliptin and metformin immediate-release has been studied in patients with type 2 diabetes inadequately controlled on diet and exercise and in combination with other antidiabetic medications.

There have been no clinical efficacy or safety studies conducted with SITAGLIPTIN + METFORMIN HCL XR to characterize its effect on hemoglobin A1c (A1C) reduction. Bioequivalence of SITAGLIPTIN + METFORMIN HCL XR tablets with coadministered sitagliptin and extended-release metformin tablets has been demonstrated for all tablet strengths

Metformin Extended-Release Compared to Metformin Immediate-Release in Patients with Type 2 Diabetes

In a multicenter, randomized, double-blind, active-controlled, dose-ranging, parallel group trial extended-release metformin HCl 1500 mg once daily, extended-release metformin HCl 1500 mg per day in divided doses (500 mg in the morning and 1000 mg in the evening), and extended-release metformin HCl 2000 mg once daily were compared to immediate-release metformin HCl 1500 mg per day in divided doses (500 mg in the morning and 1000 mg in the evening). This trial enrolled patients (n = 338) who were newly diagnosed with diabetes, patients treated only with diet and exercise, patients treated with a single anti-diabetic medication (sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglitinides), and patients (n = 368) receiving metformin HCl up to 1500 mg/day plus a sulfonylurea at a dose equal to or less than one-half the maximum dose. Patients who were enrolled on monotherapy or combination antidiabetic therapy underwent a 6-week washout. Patients randomized to extended-release metformin HCl began titration from 1000 mg/day up to their assigned treatment dose over 3 weeks. Patients randomized to immediate-release metformin HCl initiated 500 mg twice daily for 1 week followed by 500 mg with breakfast and 1000 mg with dinner for the second week. The 3-week treatment period was followed by an additional 21-week period at the randomized dose. For HbA1c and fasting plasma glucose, each of the extended-release metformin regimens was at least as effective as immediate-release metformin. Additionally, once daily dosing of extended-release metformin was as effective as twice daily dosing of the immediate-release metformin formulation.

Sitagliptin and Metformin Immediate-Release Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise

A total of 1091 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind, placebo-controlled factorial study designed to assess the efficacy of sitagliptin and metformin immediate-release coadministration. Patients on an antihyperglycemic agent (N=541) underwent a diet, exercise, and drug washout period of up to 12 weeks duration. After the washout period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized after completing a 2-week single-blind placebo run-in period. Patients not on antihyperglycemic agents at study entry (N=550) with inadequate glycemic control (A1C 7.5% to 11%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. Approximately equal numbers of patients were randomized to receive placebo, 100 mg of sitagliptin once daily, 500 mg or 1000 mg of metformin HCl immediate-release twice daily, or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin HCl immediate-release twice daily. Patients who failed to meet specific glycemic goals during the study were treated with glyburide (glibenclamide) rescue.

Sitagliptin and metformin immediate-release coadministration provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin immediate-release alone, and to sitagliptin alone. For patients not on an antihyperglycemic agent at study entry, mean reductions from baseline in A1C were: sitagliptin 100 mg once daily, -1.1%; metformin HCl immediate-release 500 mg bid, -1.1%; metformin HCl immediate-release 1000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin HCl immediate-release 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin HCl immediate-release 1000 mg bid, -1.9%; and for patients receiving placebo, -0.2%. Lipid effects were generally neutral. The decrease in body weight in the groups given sitagliptin in combination with metformin immediate-release was similar to that in the groups given metformin alone or placebo.

Table: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin and Metformin Immediate-Release, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise*

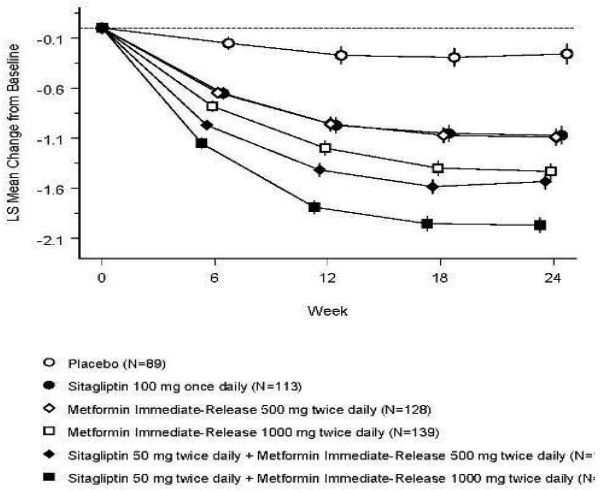
	Placebo	Sitagliptin 100 mg once daily	Metformin HCl Immediate-Release 500 mg twice daily	Metformin HCl Immediate-Release 1000 mg twice daily	Sitagliptin 50 mg bid + Metformin HCl Immediate-Release 500 mg twice daily	Sitagliptin 50 mg bid + Metformin HCl Immediate-Release 1000 mg twice daily
A1C (%)	**N = 165**	**N = 175**	**N = 178**	**N = 177**	**N = 183**	**N = 178**
Baseline (mean)	8.7	8.9	8.9	8.7	8.8	8.8
Change from baselin	0.2	-0.7	-0.8	-1.1	-1.4	-1.9

e (adjusted mean†)						
Difference from placebo (adjusted mean†) (95% CI)		-0.8‡ (-1.1, -0.6)	-1.0‡ (-1.2, -0.8)	-1.3‡ (-1.5, -1.1)	-1.6‡ (-1.8, -1.3)	-2.1‡ (-2.3, -1.8)
Patients (%) achieving A1C <7%	15 (9%)	35 (20%)	41 (23%)	68 (38%)	79 (43%)	118 (66%)
% Patients receiving rescue medication	32	21	17	12	8	2
FPG (mg/dL)	**N = 169**	**N = 178**	**N = 179**	**N = 179**	**N = 183**	**N = 180**
Baseline (mean)	196	201	205	197	204	197
Change from baseline (adjusted mean†)	6	-17	-27	-29	-47	-64
Difference from placebo (adjusted mean†) (95% CI)		-23‡ (-33, -14)	-33‡ (-43, -24)	-35‡ (-45, -26)	-53‡ (-62, -43)	-70‡ (-79, -60)
2-hour PPG (mg/dL)	**N = 129**	**N = 136**	**N = 141**	**N = 138**	**N = 147**	**N = 152**
Baseline (mean)	277	285	293	283	292	287
Change from baseline (adjusted mean†)	0	-52	-53	-78	-93	-117
Difference from placebo (adjusted mean†) (95% CI)		-52‡ (-67, -37)	-54‡ (-69, -39)	-78‡ (-93, -63)	-93‡ (-107, -78)	-117‡ (-131, -102)

* Intent-to-treat population using last observation on study prior to glyburide (glibenclamide) rescue therapy.
†Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
‡ p<0.001 compared to placebo.

The Completers Population: least squares means adjusted for prior antihyperglycemic therapy and baseline value.

Figure 1: Mean Change from Baseline for A1C (%) over 24 Weeks with Sitagliptin and Metformin Immediate-Release, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled with Diet and Exercise*



Initial combination therapy or maintenance of combination therapy should be individualized and are left to the discretion of the health care provider.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Immediate-Release Alone

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin immediate-release. Patients already on metformin HCl immediate-release (N=431) at a dose of at least 1500 mg per day were randomized after completing a 2-week, single-blind placebo run-in period. Patients on metformin immediate-release and another antihyperglycemic agent (N=229) and patients not on any antihyperglycemic agents (off therapy for at least 8 weeks, N=41) were randomized after a run-in period of approximately 10 weeks on metformin HCl immediate-release (at a dose of at least 1500 mg per day) in monotherapy. Patients were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

In combination with metformin immediate-release, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin immediate-release. Rescue glycemic therapy was used in 5% of patients treated with sitagliptin 100 mg and 14% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table: Glycemic Parameters at Final Visit (24-Week Study) of Sitagliptin as Add-on Combination Therapy with Metformin Immediate-Release*

	Sitagliptin 100 mg once daily + Metformin Immediate-Release	**Placebo + Metformin Immediate-Release**
A1C (%)	**N = 453**	**N = 224**
Baseline (mean)	8.0	8.0
Change from baseline (adjusted mean†)	-0.7	-0.0
Difference from placebo + metformin immediate-release (adjusted mean†) (95% CI)	-0.7‡ (-0.8, -0.5)	
Patients (%) achieving A1C <7%	213 (47%)	41 (18%)
FPG (mg/dL)	**N = 454**	**N = 226**
Baseline (mean)	170	174
Change from baseline (adjusted mean†)	-17	9

Difference from placebo + metformin immediate-release (adjusted mean†) (95% CI)	-25‡ (-31, -20)	
2-hour PPG (mg/dL)	**N = 387**	**N = 182**
Baseline (mean)	275	272
Change from baseline (adjusted mean†)	-62	-11
Difference from placebo + metformin immediate-release (adjusted mean†) (95% CI)	-51‡ (-61, -41)	

*Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy.
†Least squares means adjusted for prior antihyperglycemic therapy and baseline value.
‡p<0.001 compared to placebo + metformin.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin Immediate-Release and Glimepiride

A total of 441 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with glimepiride, with or without metformin immediate-release. Patients entered a run-in treatment period on glimepiride (≥4 mg per day) alone or glimepiride in combination with metformin HCl immediate-release (≥1500 mg per day). After a dose-titration and dose-stable run-in period of up to 16 weeks and a 2-week placebo run-in period, patients with inadequate glycemic control (A1C 7.5% to 10.5%) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

Patients receiving sitagliptin with metformin immediate-release and glimepiride had significant improvements in A1C and FPG compared to patients receiving placebo with metformin immediate-release and glimepiride, with mean reductions from baseline relative to placebo in A1C of -0.9% and in FPG of -21 mg/dL. Rescue therapy was used in 8% of patients treated with add-on sitagliptin 100 mg and 29% of patients treated with add-on placebo. The patients treated with add-on sitagliptin had a mean increase in body weight of 1.1 kg vs. add-on placebo (+0.4 kg vs. -0.7 kg). In addition, add-on sitagliptin resulted in an increased rate of hypoglycemia compared to add-on placebo.

Table: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin in Combination with Metformin Immediate-Release and Glimepiride*

	Sitagliptin 100 mg + Metformin Immediate-Release and Glimepiride	**Placebo + Metformin Immediate-Release and Glimepiride**
A1C (%)	**N = 115**	**N = 105**
Baseline (mean)	8.3	8.3
Change from baseline (adjusted mean†)	-0.6	0.3
Difference from placebo (adjusted mean†) (95% CI)	-0.9‡ (-1.1, -0.7)	
Patients (%) achieving A1C <7%	26 (23%)	1 (1%)
FPG (mg/dL)	**N = 115**	**N = 109**
Baseline (mean)	179	179
Change from baseline (adjusted mean†)	-8	13
Difference from placebo (adjusted mean†) (95% CI)	-21‡ (-32, -10)	

*Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy.
†Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
‡ p<0.001 compared to placebo.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin Immediate-Release and Rosiglitazone

A total of 278 patients with type 2 diabetes participated in a 54-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin immediate-release and rosiglitazone. Patients on dual therapy with metformin HCl immediate-release ≥1500 mg/day and rosiglitazone ≥4 mg/day or with metformin HCl immediate-release ≥1500 mg/day and pioglitazone ≥30 mg/day (switched to rosiglitazone ≥4 mg/day) entered a dose-stable run-in period of 6 weeks. Patients on other dual therapy were switched to metformin HCl immediate-release ≥1500 mg/day and rosiglitazone ≥4 mg/day in a dose titration/stabilization run-in period of up to 20 weeks in duration. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized 2:1 to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with glipizide (or other sulfonylurea) rescue. The primary time point for evaluation of glycemic parameters was Week 18.

In combination with metformin immediate-release and rosiglitazone, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin immediate-release and rosiglitazone at Week 18. At Week 54, mean reduction in A1C was -1.0% for patients treated with sitagliptin and -0.3% for patients treated with placebo in an analysis based on the intent-to-treat population. Rescue therapy was used in 18% of patients treated with sitagliptin 100 mg and 40% of patients treated with placebo. There was no significant difference between sitagliptin and placebo in body weight change.

Table: Glycemic Parameters at Week 18 for Sitagliptin in Add-on Combination Therapy with Metformin Immediate-Release and Rosiglitazone*

	Week 18	
	Sitagliptin 100 mg + Metformin Immediate-Release + Rosiglitazone	**Placebo + Metformin Immediate-Release + Rosiglitazone**
A1C (%)	**N = 176**	**N = 93**
Baseline (mean)	8.8	8.7
Change from baseline (adjusted mean†)	-1.0	-0.4
Difference from placebo + rosiglitazone + metformin immediate-release (adjusted mean†) (95% CI)	-0.7‡ (-0.9, -0.4)	
Patients (%) achieving A1C <7%	39 (22%)	9 (10%)
FPG (mg/dL)	**N = 179**	**N = 94**
Baseline (mean)	181	182
Change from baseline (adjusted mean†)	-30	-11
Difference from placebo + rosiglitazone + metformin immediate-release (adjusted mean†) (95% CI)	-18‡ (-26, -10)	
2-hour PPG (mg/dL)	**N = 152**	**N = 80**
Baseline (mean)	256	248
Change from baseline (adjusted mean†)	-59	-21
Difference from placebo + rosiglitazone + metformin immediate-release (adjusted mean†) (95% CI)	-39‡ (-51, -26)	

*Intent-to-treat population using last observation on study prior to glipizide (or other sulfonylurea) rescue therapy.
†Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
‡p<0.001 compared to placebo + metformin + rosiglitazone.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin Immediate-Release and Insulin

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin as add-on to insulin therapy. Approximately 75% of patients were also taking metformin immediate-release. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin HCl immediate-release (≥1500 mg per day). Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a pre-mixed insulin. After the run-in period, patients with inadequate glycemic control

(A1C 7.5% to 11%) were randomized to the addition of either 100 mg of sitagliptin (N=229) or placebo (N=233), administered once daily. Patients were on a stable dose of insulin prior to enrollment with no changes in insulin dose permitted during the run-in period. Patients who failed to meet specific glycemic goals during the double-blind treatment period were to have uptitration of the background insulin dose as rescue therapy.

Among patients also receiving metformin immediate-release, the median daily insulin (pre-mixed, intermediate or long acting) dose at baseline was 40 units in the sitagliptin-treated patients and 42 units in the placebo-treated patients. The median change from baseline in daily dose of insulin was zero for both groups at the end of the study. Patients receiving sitagliptin with metformin immediate-release and insulin had significant improvements in A1C, FPG and 2-hour PPG compared to patients receiving placebo with metformin immediate-release and insuli. The adjusted mean change from baseline in body weight was -0.3 kg in patients receiving sitagliptin with metformin immediate-release and insulin and -0.2 kg in patients receiving placebo with metformin immediate-release and insulin. There was an increased rate of hypoglycemia in patients treated with sitagliptin.

Table: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin as Add-on Combination Therapy with Metformin Immediate-Release and Insulin*

	Sitagliptin 100 mg + Metformin Immediate-Release + Insulin	**Placebo + Metformin Immediate-Release + Insulin**
A1C (%)	**N = 223**	**N = 229**
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean†, ‡)	-0.7	-0.1
Difference from placebo (adjusted mean†) (95% CI)	-0.5§ (-0.7, -0.4)	
Patients (%) achieving A1C <7%	32 (14%)	12 (5%)
FPG (mg/dL)	**N = 225**	**N = 229**
Baseline (mean)	173	176
Change from baseline (adjusted mean†)	-22	-4
Difference from placebo (adjusted mean†) (95% CI)	-18§ (-28, -8.4)	
2-hour PPG (mg/dL)	**N = 182**	**N = 189**
Baseline (mean)	281	281
Change from baseline (adjusted mean†)	-39	1
Difference from placebo (adjusted mean†) (95% CI)	-40§ (-53, -28)	

*Intent-to-treat population using last observation on study prior to rescue therapy.
†Least squares means adjusted for insulin use at the screening visit, type of insulin used at the screening visit (pre-mixed vs. non pre-mixed [intermediate- or long-acting]), and baseline value.
‡Treatment by insulin stratum interaction was not significant (p>0.10).
§ p<0.001 compared to placebo.

Maintenance of Sitagliptin During Initiation and Titration of Insulin Glargine

A total of 746 patients with type 2 diabetes (mean baseline HbA1C 8.8%, disease duration 10.8 years) participated in a 30-week, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of continuing sitagliptin during the initiation and uptitration of insulin glargine. Patients who were on a stable dose of metformin HCl (≥1500 mg/day) in combination with a DPP-4 inhibitor and/or sulfonylurea but with inadequate glycemic control (A1C 7.5% to 11%) were enrolled in the study. Those on metformin and sitagliptin (100 mg/day) directly entered the double-blind treatment period; those on another DPP-4 inhibitor and/or on a sulfonylurea entered a 4-8 week run-in period in which they were maintained on metformin and switched to sitagliptin (100 mg); other DPP-4 inhibitors and sulfonylureas were discontinued. At randomization patients were randomized either to continue sitagliptin or to discontinue sitagliptin and switch to a matching placebo. On the day of randomization, insulin glargine was initiated at a dose of 10 units subcutaneously in the evening. Patients were instructed to uptitrate their insulin dose in the evening based on fasting blood glucose measurements to achieve a target of 72-100 mg/dL.

At 30 weeks, the mean reduction in A1C was greater in the sitagliptin group than in the placebo group. At the end of the trial, 27.3% of patients in the sitagliptin group and 27.3% in the placebo group had a fasting plasma glucose (FPG) in the target range; there was no significant difference in insulin dose between arms.

Table: Change from Baseline in A1C and FPG at Week 30 in the Maintenance of Sitagliptin During Initiation and Titration of Insulin Glargine Study

	Sitagliptin 100 mg+Metformin+ Insulin Glargine	**Placebo+Metformin+ Insulin Glargine**
A1C (%)	**N = 373***	**N = 370***
Baseline (mean)	8.8	8.8
Week 30 (mean)	6.9	7.3
Change from baseline (adjusted mean)†	-1.9	-1.4
Difference from placebo (adjusted mean) (95% CI)†	-0.4 (-0.6, -0.3)‡	
Patients (%) with A1C <7%	202 (54.2%)	131 (35.4%)
FPG (mg/dL)	**N = 373***	**N = 370***
Baseline (mean)	199	201
Week 30 (mean)	118	123
Change from baseline (adjusted mean)†	-81	-76

*N is the number of randomized and treated patients.
†Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputation to model washout of the treatment effect using placebo data for all subjects having missing Week 30 data.
‡p<0.001 compared to placebo.

Sitagliptin Add-on Therapy vs. Glipizide Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Immediate-Release

The efficacy of sitagliptin was evaluated in a 52-week, double-blind, glipizide-controlled noninferiority trial in patients with type 2 diabetes. Patients not on treatment or on other antihyperglycemic agents entered a run-in treatment period of up to 12 weeks duration with metformin HCl immediate-release monotherapy (dose of ≥1500 mg per day) which included washout of medications other than metformin immediate-release, if applicable. After the run-in period, those with inadequate glycemic control (A1C 6.5% to 10%) were randomized 1:1 to the addition of sitagliptin 100 mg once daily or glipizide for 52 weeks. Patients receiving glipizide were given an initial dosage of 5 mg/day and then electively titrated over the next 18 weeks to a maximum dosage of 20 mg/day as needed to optimize glycemic control. Thereafter, the glipizide dose was to be kept constant, except for down-titration to prevent hypoglycemia. The mean dose of glipizide after the titration period was 10 mg.

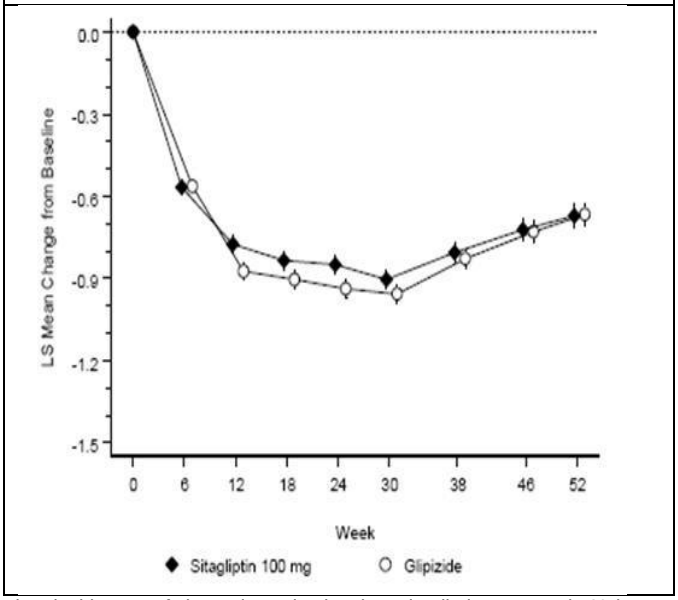
After 52 weeks, sitagliptin and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis. These results were consistent with the per protocol analysis (Figure 2). A conclusion in favor of the non-inferiority of sitagliptin to glipizide may be limited to patients with baseline A1C comparable to those included in the study (over 70% of patients had baseline A1C <8% and over 90% had A1C <9%).

Table: Glycemic Parameters in a 52-Week Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin Immediate-Release (Intent-to-Treat Population) *

	Sitagliptin 100 mg + Metformin Immediate-Release	**Glipizide + Metformin Immediate-Release**
A1C (%)	**N = 576**	**N = 559**
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean†)	-0.5	-0.6
FPG (mg/dL)	**N = 583**	**N = 568**
Baseline (mean)	166	164
Change from baseline (adjusted mean†)	-8	-8

* The per protocol population (mean baseline A1C of 7.5%) included patients without major protocol violations who had observations at baseline and at Week 52.
* The intent-to-treat analysis used the patients' last observation in the study prior to discontinuation.
† Least squares means adjusted for prior antihyperglycemic therapy status and baseline A1C value.

**Figure 2: Mean Change from Baseline for A1C (%) Over 52 Weeks in a Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin Immediate-Release (Per Protocol Population)*



The incidence of hypoglycemia in the sitagliptin group (4.9%) was significantly (p<0.001) lower than that in the glipizide group (32.0%). Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs. +1.1 kg).

PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

SITAGLIPTIN + METFORMIN HCL XR
No animal studies have been conducted with the combined products in SITAGLIPTIN + METFORMIN HCL XR to evaluate carcinogenesis, mutagenesis or impairment of fertility. The following data are based on the findings in studies with sitagliptin and metformin individually.
Sitagliptin
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 in females were observed (approximately 25- and 100-times human exposure at the MRHD based on AUC comparison).
Metformin
Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses up to 2000 mg applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and *in vivo* mouse micronucleus tests were negative. Fertility of male or female rats was not affected by metformin when administered at doses up to 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

PRESENTATION

Jentin Met XR 50mg+500mg tablets are available in alu-alu blister pack of 14 Tablets.

Jentin Met XR 50mg+1000mg tablets are available in alu-alu blister pack of 14 Tablets.

Jentin Met XR 100mg+1000mg tablets are available in alu-alu blister pack of 14 Tablets.

INSTRUCTIONS

-To be sold on the prescription of a registered medical practitioner only.

- Protect from sunlight, moisture & heat.

- Store below 30°C.

- Keep all medicines out of sight & reach of children.

REGISTRATION NUMBER

Jentin Met XR 50mg+500mg: 107732

Jentin Met XR 50mg+1000mg: 107759

Jentin Met XR 100mg+1000mg: 107760

MANUFACTURING LICENSE NUMBER: 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter

Manufactured by:

The Searle Company Limited,

F-319, S.I.T.E., Karachi-Pakistan.

DATE OF PUBLICATION OF THE PACKAGE INSERT

June 2021

SPL/SPC-JMXR.T/621-000(001)