1. NAME OF THE MEDICINAL PRODUCT
SITAGLIPTIN SANDOZ FILM COATED TABLET 50 MG
SITAGLIPTIN SANDOZ FILM COATED TABLET 100 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each SITAGLIPTIN SANDOZ FILM COATED TABLET 50 MG contains sitagliptin (as phosphate monohydrate) 50mg.
Each SITAGLIPTIN SANDOZ FILM COATED TABLET 100 MG contains sitagliptin (as phosphate monohydrate) 100mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film coated tablet.

SITAGLIPTIN SANDOZ FILM COATED TABLET 50 MG
Pink, round, biconvex, film-coated tablet debossed with “SN” on one side and “50” on the other side.

SITAGLIPTIN SANDOZ FILM COATED TABLET 100 MG
Brown, round, biconvex, film-coated tablet debossed with “SN” on one side and “100” on the other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Monotherapy
Sitagliptin Sandoz is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Combination with Metformin
Sitagliptin Sandoz is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin as initial therapy or when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

Combination with a Sulfonylurea
Sitagliptin Sandoz is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a sulfonylurea when treatment with the single agent alone, with diet and exercise, does not provide adequate glycemic control.

Combination with a PPARγ agonist
Sitagliptin Sandoz is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a PPARγ agonist (e.g., thiazolidinediones) when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

Combination with Metformin and a Sulfonylurea
Sitagliptin Sandoz is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea when dual therapy with these agents, with diet and exercise, does not provide adequate glycemic control.

Combination with Insulin
Sitagliptin Sandoz is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycemic control.

Important Limitations of Use

Sitagliptin Sandoz 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 Sandoz 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 Sandoz (see section 4.4).

4.2 Posology and method of administration

Recommended Dosing

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

Patients with Renal Impairment

Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of Sitagliptin Sandoz and periodically thereafter.

For patients with mild renal impairment (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2), no dosage adjustment for Sitagliptin Sandoz is required.

For patients with moderate renal impairment (eGFR ≥ 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2), no dosage adjustment for Sitagliptin Sandoz is required.

For patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2), the dose of Sitagliptin Sandoz is 50 mg once daily.

For patients with severe renal impairment (eGFR ≥ 15 mL/min/1.73 m^2 to < 30 mL/min/1.73 m^2) or with end-stage renal disease (ESRD) (eGFR < 15 mL/min/1.73 m^2), including those requiring hemodialysis or peritoneal dialysis, the dose of Sitagliptin Sandoz is 25 mg once daily. Sitagliptin Sandoz may be administered without regard to the timing of dialysis.

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

When Sitagliptin Sandoz 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 (see section 4.4).

Pediatric Use

Sitagliptin should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy.

A 54-week, double-blind study was conducted to evaluate the efficacy and safety of sitagliptin in pediatric patients (10 to 17 years of age) with type 2 diabetes who were not on anti-hyperglycaemic therapy for at least 12 weeks or were on a stable dose of insulin for at least 12 weeks. Patients were randomized and treated with sitagliptin 100 mg (N=95) or placebo (N=95) once daily for 20 weeks.

Treatment with sitagliptin 100 mg did not provide significant improvement in HbA_{1c} at 20 weeks.

In pediatric patients aged 10 to 17 years with type 2 diabetes, the profile of side effects was comparable to that observed in adults.

Sitagliptin has not been studied in pediatric patients under 10 years of age.

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 (see sections 4.2 and 5.2).

Method of administration
For oral administration.
Sitagliptin Sandoz can be taken with or without food.

4.3 Contraindications
History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use
Pancreatitis
There have been 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.

Use in Patients with Renal Impairment
A dosage adjustment is recommended in patients with eGFR< 45 mL/min/1.73 m^2 and in patients with ESRD requiring hemodialysis or peritoneal dialysis (see sections 4.2 and 5.2).

Use with Medications Known to Cause Hypoglycemia
As is typical with other antihyperglycemic agents, hypoglycemia has been observed when sitagliptin was used in combination with insulin or a sulfonylurea (see section 4.8). Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia (see sections 4.2).

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 (see section 4.8).

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

Severe and Disabling Arthralgia
There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

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

4.5 Interaction with other medicinal products and other forms of interaction
Digoxin
There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (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 Sandoz is recommended.

See also section 5.2.

4.6 Pregnancy and lactation
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.

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 post-dose. 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 Sandoz is administered to a nursing woman.

4.7 Effects on ability to drive and use machines
Sitagliptin has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been

reported. In addition, patients should be alerted to the risk of hypoglycaemia when sitagliptin is used in combination with a sulphonylurea or with insulin.

4.8 Undesirable effects

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.

In controlled clinical studies as both monotherapy and combination therapy with metformin, or pioglitazone, 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 (see Table 3); the incidence of discontinuation due to clinical adverse reactions was similar to placebo.

Two placebo-controlled monotherapy studies, one of 18- and one of 24-week duration, included patients treated with sitagliptin 100 mg daily, sitagliptin 200 mg daily, and placebo. Four placebo-controlled add-on combination therapy studies were also conducted: one with metformin; one with pioglitazone, one with glimepiride (with or without metformin); and one with insulin (with or without metformin). In these trials, patients with inadequate glycemic control on a stable dose of the background therapy were randomized to add-on therapy with sitagliptin 100 mg daily or placebo. The adverse reactions, excluding hypoglycemia, reported regardless of investigator assessment of causality in ≥ 5% of patients treated with sitagliptin 100 mg daily and more commonly than in patients treated with placebo, are shown in Table 1 for the clinical trials of at least 18 weeks duration. Incidences of hypoglycemia are shown in Table 3.

Table 1: Placebo-Controlled Clinical Studies of Sitagliptin Monotherapy or Add-on Combination Therapy with Pioglitazone or Glimepiride +/- Metformin: Adverse Reactions (Excluding Hypoglycemia) Reported in ≥ 5% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality†

	Number of Patients (%)	
Monotherapy (18 or 24 weeks)	**Sitagliptin 100 mg**	**Placebo**
	N = 443	N = 363
Nasopharyngitis	23 (5.2)	12 (3.3)
Combination with Pioglitazone (24 weeks)	**Sitagliptin 100 mg + Pioglitazone**	**Placebo + Pioglitazone**
	N = 175	N = 178
Upper Respiratory Tract Infection	11 (6.3)	6 (3.4)
Headache	9 (5.1)	7 (3.9)
Combination with Glimepiride (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg +Glimepiride (+/- Metformin)**	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Nasopharyngitis	14 (6.3)	10 (4.6)
Headache	13 (5.9)	5 (2.3)

† Intent to treat population

In the 24-week study of patients receiving sitagliptin as add-on combination therapy with metformin, there were no adverse reactions reported regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients given placebo.

In the 24-week study of patients receiving sitagliptin as add-on therapy to stable-dose insulin (with or without metformin), there were no adverse reactions reported regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients given placebo, except for hypoglycemia (see Table 3). In another 24-week study of patients receiving sitagliptin as add-on therapy while undergoing insulin intensification (with or without metformin), the only adverse experience reported regardless of investigator assessment of causality in ≥ 5% of patients treated with sitagliptin and more commonly than in patients treated with placebo was diarrhea (sitagliptin 5.2%; placebo 3.3%).

In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the incidence of selected gastrointestinal adverse reactions in patients treated with sitagliptin was as follows: abdominal pain (sitagliptin 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), and diarrhea (3.0%, 2.3%).

In an additional, 24-week, placebo-controlled factorial study of initial therapy with sitagliptin in combination with metformin, the adverse reactions reported (regardless of investigator assessment of causality) in ≥ 5% of patients are shown in Table 2.

Table 2: Initial Therapy with Combination of Sitagliptin and Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥ 5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Metformin alone, Sitagliptin alone, and Placebo)†

	Number of Patients (%)			
	Placebo	**Sitagliptin 100 mg QD**	**Metformin 500 or 1000 mg bid††**	**Sitagliptin 50 mg bid + Metformin 500 or 1000 mg bid††**
	N = 176	**N = 179**	**N = 364††**	**N = 372††**
Upper Respiratory Infection	9 (5.1)	8 (4.5)	19 (5.2)	23 (6.2)
Headache	5 (2.8)	2 (1.1)	14 (3.8)	22 (5.9)

† Intent-to-treat population.
†† Data pooled for the patients given the lower and higher doses of metformin.

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with sitagliptin.

In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of non-adjudicated acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control) (see section 4.4). See also TECOS Cardiovascular Safety Study, below.

TECOS Cardiovascular Safety Study
The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline estimated glomerular filtration rate (eGFR) was ≥30 and <50 mL/min/1.73 m^2), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA_{1c} and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo. Assessment of pre-specified diabetes-related complications revealed similar incidences between groups including infections (18.4% of the

sitagliptin-treated patients and 17.7% of the placebo-treated patients) and renal failure (1.4% of sitagliptin-treated patients and 1.5% of placebo-treated patients). The study population included a total of 2,004 patients ≥75 years of age (970 treated with sitagliptin and 1,034 treated with placebo). The adverse event profile in patients ≥75 years of age was generally similar to the overall population.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 2.7% in sitagliptin-treated patients and 2.5% in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 1.0% in sitagliptin-treated patients and 0.7% in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3% in sitagliptin-treated patients and 0.2% in placebo-treated patients. The incidence of adjudication-confirmed malignancy events was 3.7% in sitagliptin-treated patients and 4.0% in placebo-treated patients.

Pediatric Population
In clinical trials with sitagliptin in pediatric patients with type 2 diabetes mellitus aged 10 to 17 years, the profile of adverse reactions was comparable to that observed in adults.

Hypoglycemia
In all (N=9) studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia. A concurrent blood glucose measurement was not required although most (74%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤ 70 mg/dL. When sitagliptin was co-administered with a sulfonylurea or with insulin, the percentage of patients with at least one adverse reaction of hypoglycemia was higher than in the corresponding placebo group (Table 3).

Table 3: Incidence and Rate of Hypoglycemia† in Placebo-Controlled Clinical Studies when Sitagliptin was used as Add-On Therapy to Glimepiride (with or without Metformin) or Insulin (with or without Metformin), Regardless of Investigator Assessment of Causality

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

†Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required; intent to treat population.
‡ Based on total number of events (i.e., a single patient may have had multiple events).
§ Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

In the 24-week, placebo-controlled factorial study of initial therapy with sitagliptin in combination with metformin, the incidence of hypoglycemia was 0.6% in patients given placebo, 0.6% in patients

given sitagliptin alone, 0.8% in patients given metformin alone, and 1.6% in patients given sitagliptin in combination with metformin.

Laboratory Tests
Across clinical studies, the incidence of laboratory adverse reactions was similar in patients treated with sitagliptin 100 mg compared to patients treated with placebo. A small increase in white blood cell count (WBC) was observed due to an increase in neutrophils. This increase in WBC (of approximately 200 cells/microL vs placebo, in four pooled placebo-controlled clinical studies, with a mean baseline WBC count of approximately 6600 cells/microL) is not considered to be clinically relevant. In a 12-week study of 91 patients with chronic renal insufficiency, 37 patients with moderate renal insufficiency were randomized to sitagliptin 50 mg daily, while 14 patients with the same magnitude of renal impairment were randomized to placebo. Mean (SE) increases in serum creatinine were observed in patients treated with sitagliptin [0.12 mg/dL (0.04)] and in patients treated with placebo [0.07 mg/dL (0.07)]. The clinical significance of this added increase in serum creatinine relative to placebo is not known.

Postmarketing Experience
Additional adverse reactions have been identified during postapproval use of sitagliptin as monotherapy and/or in combination with other antihyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome (see section 4.4); hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see sections 4.1 and 4.4); worsening renal function, including acute renal failure (sometimes requiring dialysis) and tubulointerstitial nephritis; bullous pemphigoid (see sections 4.4); severe and disabling arthralgia (see sections 4.4); constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus.

4.9 Overdose
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 section 5.1). There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy as dictated by the patient's clinical status.

Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drugs used in diabetes, Dipeptidyl peptidase 4 (DPP-4) inhibitors.
ATC code: A10BH01.

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. Co-administration 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 post-dose and was 8.0 msec. This increase is not considered to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100 mg dose.

In patients with type 2 diabetes administered sitagliptin 100 mg (N=81) or sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

CLINICAL STUDIES

There were approximately 5200 patients with type 2 diabetes randomized in nine double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of sitagliptin on glycemic control. In a pooled analysis of seven of these studies, the ethnic/racial distribution was approximately 59% white, 20% Hispanic, 10% Asian, 6% black, and 6% other groups. Patients had an overall mean age of approximately 55 years (range 18 to 87 years). In addition, an active (glipizide)-

controlled study of 52-weeks duration was conducted in 1172 patients with type 2 diabetes who had inadequate glycemic control on metformin.

In patients with type 2 diabetes, treatment with sitagliptin produced clinically significant improvements in hemoglobin A1C, fasting plasma glucose (FPG) and 2-hour post-prandial glucose (PPG) compared to placebo.

Monotherapy

A total of 1262 patients with type 2 diabetes participated in two double-blind, placebo-controlled studies, one of 18-week and another of 24-week duration, to evaluate the efficacy and safety of sitagliptin monotherapy. In both monotherapy studies, patients currently on an antihyperglycemic agent discontinued the agent, and underwent a diet, exercise, and drug wash-out period of about 7 weeks. Patients with inadequate glycemic control (A1C 7% to 10%) after the washout period were randomized after completing a 2-week single-blind placebo run-in period; patients not currently on antihyperglycemic agents (off therapy for at least 8 weeks) with inadequate glycemic control (A1C 7% to 10%) were randomized after completing the 2-week single-blind placebo run-in period. In the 18-week study, 521 patients were randomized to placebo, sitagliptin 100 mg, or sitagliptin 200 mg, and in the 24-week study 741 patients were randomized to placebo, sitagliptin 100 mg, or sitagliptin 200 mg. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue, added on to placebo or sitagliptin.

Treatment with sitagliptin at 100 mg daily provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo (Table 4). In the 18-week study, 9% of patients receiving sitagliptin 100 mg and 17% who received placebo required rescue therapy. In the 24-week study, 9% of patients receiving sitagliptin 100 mg and 21% of patients receiving placebo required rescue therapy. The improvement in A1C compared to placebo was not affected by gender, age, race, prior antihyperglycemic therapy, or baseline BMI. As is typical for trials of agents to treat type 2 diabetes, the mean reduction in A1C with sitagliptin appears to be related to the degree of A1C elevation at baseline. In these 18- and 24-week studies, among patients who were not on an antihyperglycemic agent at study entry, the reductions from baseline in A1C were -0.7% and -0.8%, respectively, for those given sitagliptin, and -0.1% and -0.2%, respectively, for those given placebo. Overall, the 200 mg daily dose did not provide greater glycemic efficacy than the 100 mg daily dose. The effect of sitagliptin on lipid endpoints was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy in either study, compared to a small reduction in patients given placebo.

Table 4: Glycemic Parameters in 18- and 24-Week Placebo-Controlled Studies of Sitagliptin in Patients with Type 2 Diabetes[†]

	18-Week Study		**24-Week Study**	
	Sitagliptin 100 mg	**Placebo**	**Sitagliptin 100 mg**	**Placebo**
A1C (%)	**N = 193**	**N = 103**	**N = 229**	**N = 244**
Baseline (mean)	8.0	8.1	8.0	8.0
Change from baseline (adjusted mean[‡])	-0.5	0.1	-0.6	0.2
Difference from placebo (adjusted mean[‡]) (95% CI)	-0.6[§] (-0.8, -0.4)		-0.8[§] (-1.0, -0.6)	
Patients (%) achieving A1C <7%	69 (36%)	16 (16%)	93 (41%)	41 (17%)
FPG (mg/dL)	**N = 201**	**N = 107**	**N = 234**	**N = 247**
Baseline (mean)	180	184	170	176
Change from baseline (adjusted mean[‡])	-13	7	-12	5
Difference from placebo (adjusted mean[‡]) (95% CI)	-20[§] (-31, -9)		-17[§] (-24, -10)	

2-hour PPG (mg/dL)	‖	‖	**N = 201**	**N = 204**
Baseline (mean)			257	271
Change from baseline (adjusted mean‡)			49	-2
Difference from placebo (adjusted mean‡) (95% CI)			-47§ (-59, -34)	

† Intent to Treat Population using last observation on study prior to metformin rescue therapy.
‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
§ p<0.001 compared to placebo.
‖ Data not available.

Additional Monotherapy Study
A multinational, randomized, double-blind, placebo-controlled study was also conducted to assess the safety and tolerability of sitagliptin in 91 patients with type 2 diabetes and chronic renal insufficiency (creatinine clearance <50 mL/min). Patients with moderate renal insufficiency received 50 mg daily of sitagliptin and those with severe renal insufficiency or with ESRD on hemodialysis or peritoneal dialysis received 25 mg daily. In this study, the safety and tolerability of sitagliptin were generally similar to placebo. A small increase in serum creatinine was reported in patients with moderate renal insufficiency treated with sitagliptin relative to those on placebo. In addition, the reductions in A1C and FPG with sitagliptin compared to placebo were generally similar to those observed in other monotherapy studies (see section 5.2).

Combination Therapy
Add-on Combination Therapy with Metformin
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. Patients already on metformin (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 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 (at a dose of at least 1500 mg per day) in monotherapy. Patients with inadequate glycemic control (A1C 7% to 10%) 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, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin (Table 5). 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 5: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin in Add-on Combination Therapy with Metformin†

	Sitagliptin 100 mg + Metformin	**Placebo + Metformin**
A1C (%)	**N = 453**	**N = 224**
Baseline (mean)	8.0	8.0
Change from baseline (adjusted mean‡)	-0.7	-0.0
Difference from placebo + metformin (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 (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 (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.

Initial Combination Therapy with Metformin
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 as initial therapy in combination with metformin. Patients on an antihyperglycemic agent (N=541) discontinued the agent, and 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 initial therapy with placebo, 100 mg of sitagliptin once daily, 500 mg or 1000 mg of metformin twice daily, or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients who failed to meet specific glycemic goals during the study were treated with glyburide (glibenclamide) rescue.

Initial therapy with the combination of sitagliptin and metformin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to sitagliptin alone (Table 6, Figure 1). Mean reductions from baseline in A1C were generally greater for patients with higher baseline A1C values. 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 500 mg bid, -1.1%; metformin 1000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin 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 was similar to that in the groups given metformin alone or placebo.

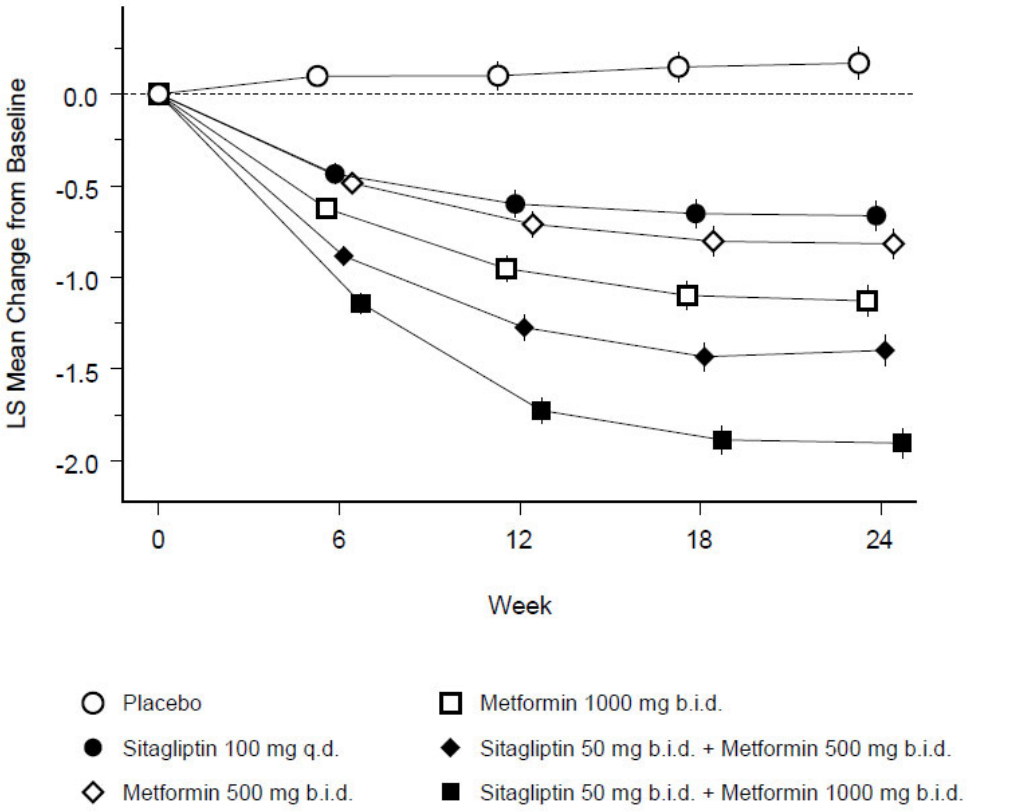
Table 6: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin and Metformin, Alone and in Combination as Initial Therapy†

	Placebo	**Sitagliptin 100 mg QD**	**Metformin 500 mg bid**	**Metformin 1000 mg bid**	**Sitagliptin 50 mg bid + Metformin 500 mg bid**	**Sitagliptin 50 mg bid + Metformin 1000 mg bid**
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 baseline (adjusted mean‡)	0.2	-0.7	-0.8	-1.1	-1.4	-1.9
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	32	21	17	12	8	2

rescue medication						
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.

Figure 1: Mean Change from Baseline for A1C (%) over 24 Weeks with Sitagliptin and Metformin, Alone and in Combination as Initial Therapy in Patients with Type 2 Diabetes†



† All Patients Treated Population Least squares means adjusted for prior antihyperglycemic therapy and baseline value.

Initial combination therapy or maintenance of combination therapy may not be appropriate for all patients. These management options are left to the discretion of the health care provider.

Active-Controlled Study vs Glipizide in Combination with Metformin

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 monotherapy (dose of ≥ 1500 mg per day) which included washout of medications other than metformin, 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.

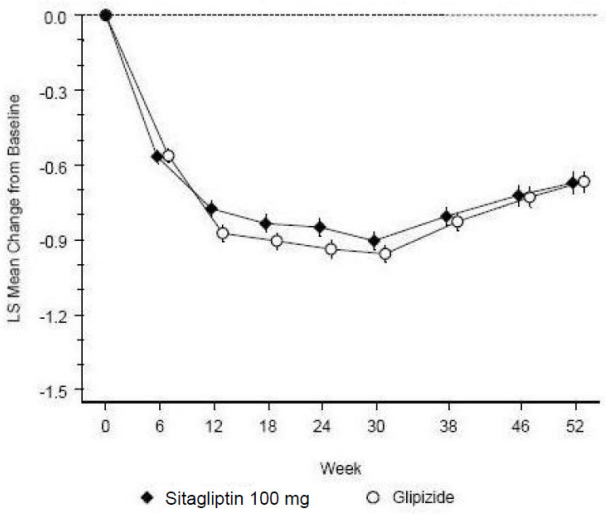
After 52 weeks, sitagliptin and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis (Table 7). These results were consistent with the per protocol analysis (Figure 2). A conclusion in favor of the non-inferiority of sitagliptin to glipizide may be limited to patients 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 7: Glycemic Parameters in a 52-Week Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin (Intent-to-Treat Population)†

	Sitagliptin 100 mg	**Glipizide**
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 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 (Per Protocol Population)†



† 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 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).

Add-on Combination Therapy with Pioglitazone

A total of 353 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 pioglitazone. Patients on any oral antihyperglycemic agent in monotherapy (N=212) or on a PPARγ agent in combination therapy (N=106) or not on an antihyperglycemic agent (off therapy for at least 8 weeks, N=34) were switched to monotherapy with pioglitazone (at a dose of 30-45 mg per day), and completed a run-in period of approximately 12 weeks in duration. After the run-in period on pioglitazone monotherapy, patients with inadequate glycemic control (A1C 7% to 10%) 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 metformin rescue. Glycemic endpoints measured were A1C and fasting glucose.

In combination with pioglitazone, sitagliptin provided significant improvements in A1C and FPG compared to placebo with pioglitazone (Table 8). Rescue therapy was used in 7% of patients treated with sitagliptin 100 mg and 14% of patients treated with placebo. There was no significant difference between sitagliptin and placebo in body weight change.

Table 8: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin in Add-on Combination Therapy with Pioglitazone†

	Sitagliptin 100 mg + Pioglitazone	**Placebo + Pioglitazone**
A1C (%)	**N = 163**	**N = 174**
Baseline (mean)	8.1	8.0
Change from baseline (adjusted mean‡)	-0.9	-0.2
Difference from placebo + pioglitazone (adjusted mean‡) (95% CI)	-0.7§ (-0.9, -0.5)	
Patients (%) achieving A1C <7%	74 (45%)	40 (23%)
FPG (mg/dL)	**N = 163**	**N = 174**
Baseline (mean)	168	166

Change from baseline (adjusted mean‡)	-17	1
Difference from placebo + pioglitazone (adjusted mean‡) (95% CI)	-18§ (-24, -11)	

† Intent to Treat Population using last observation on study prior to metformin rescue therapy.
‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
§ p<0.001 compared to placebo + pioglitazone.

Add-on Combination Therapy with Glimepiride, with or without Metformin
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. Patients entered a run-in treatment period on glimepiride (≥4 mg per day) alone or glimepiride in combination with metformin (≥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.

In combination with glimepiride, with or without metformin, sitagliptin provided significant improvements in A1C and FPG compared to placebo (Table 9). In the entire study population (patients on sitagliptin in combination with glimepiride and patients on sitagliptin in combination with glimepiride and metformin), a mean reduction from baseline relative to placebo in A1C of -0.7% and in FPG of -20 mg/dL was seen. Rescue therapy was used in 12% of patients treated with sitagliptin 100 mg and 27% of patients treated with placebo. In this study, patients treated with sitagliptin had a mean increase in body weight of 1.1 kg vs. placebo (+0.8 kg vs. -0.4 kg). In addition, there was an increased rate of hypoglycemia (see sections 4.4 and 4.8).

Table 9: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin as Add-On Combination Therapy with Glimepiride, with or without Metformin†

	Sitagliptin 100 mg + Glimepiride	**Placebo + Glimepiride**	**Sitagliptin 100 mg + Glimepiride + Metformin**	**Placebo + Glimepiride + Metformin**
A1C (%)	**N = 102**	**N = 103**	**N = 115**	**N = 105**
Baseline (mean)	8.4	8.5	8.3	8.3
Change from baseline (adjusted mean‡)	-0.3	0.3	-0.6	0.3
Difference from placebo (adjusted mean‡) (95% CI)	-0.6§ (-0.8, -0.3)		-0.9§ (-1.1, -0.7)	
Patients (%) achieving A1C <7%	11 (11%)	9 (9%)	26 (23%)	1 (1%)
FPG (mg/dL)	**N = 104**	**N = 104**	**N = 115**	**N = 109**
Baseline (mean)	183	185	179	179
Change from baseline (adjusted mean‡)	-1	18	-8	13
Difference from placebo (adjusted mean‡) (95% CI)	-19‖ (-32, -7)		-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.

‖ p<0.01 compared to placebo.

Add-on Combination Therapy with Insulin (with or without Metformin)

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 stable dose insulin therapy (with or without metformin). The racial distribution in this study was approximately 70% white, 18% Asian, 7% black, and 5% other groups. Approximately 14% of the patients in this study were Hispanic. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin (≥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 or placebo, 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.

The median daily insulin dose at baseline was 42 units in the patients treated with sitagliptin and 45 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. In combination with insulin (with or without metformin), sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo (Table 10). Both treatment groups had an adjusted mean increase in body weight of 0.1 kg from baseline to Week 24. There was an increased rate of hypoglycemia in patients treated with sitagliptin (see sections 4.4 and 4.8).

Table 10: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin as Add-on Combination Therapy with a Stable Dose of Insulin (with or without Metformin)†

	Sitagliptin 100 mg + Insulin (+/- Metformin)	**Placebo + Insulin (+/- Metformin)**
A1C (%)	**N = 305**	**N = 312**
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean‡)	-0.6	-0.1
Difference from placebo (adjusted mean‡,§) (95% CI)	-0.6‖ (-0.7, -0.4)	
Patients (%) achieving A1C <7%	39 (12.8%)	16 (5.1%)
FPG (mg/dL)	**N = 310**	**N = 313**
Baseline (mean)	176	179
Change from baseline (adjusted mean‡)	-18	-4
Difference from placebo (adjusted mean‡) (95% CI)	-15‖ (-23, -7)	
2-hour PPG (mg/dL)	**N= 240**	**N = 257**
Baseline (mean)	291	292
Change from baseline (adjusted mean‡)	-31	5
Difference from placebo (adjusted mean‡) (95% CI)	-36‖ (-47, -25)	

† Intent to Treat Population using last observation on study prior to rescue therapy.

‡ Least squares means adjusted for metformin use at the screening visit (yes/no), type of insulin used at the screening visit (pre-mixed vs. non-pre-mixed [intermediate- or long-acting]), and baseline value.

§ Treatment by stratum interaction was not significant (p>0.10) for metformin stratum and for insulin stratum.

‖ p<0.001 compared to placebo.

In another 24-week, randomized, double-blind, placebo-controlled study designed to assess the insulin-sparing efficacy of sitagliptin as add-on combination therapy, 660 patients with inadequate glycemic control on insulin glargine with or without metformin (≥1500 mg per day) were randomized to the addition of either 100 mg of sitagliptin (N=330) or placebo (N=330), administered once daily while undergoing intensification of insulin therapy. Baseline HbA_{1c} was 8.74% and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. Glycemic endpoints measured included HbA_{1c} and FPG.

At Week 24, the increase in daily insulin dose was 20% smaller in patients treated with sitagliptin (19 IU/day) than in patients treated with placebo (24 IU/day). The difference in insulin dose (-5 IU/day) was statistically significant (p=0.009). The reduction in HbA_{1c} in patients treated with sitagliptin and insulin (with or without metformin) was -1.31% compared to -0.87% in patients treated with placebo and insulin (with or without metformin), a difference of -0.45% [95% CI: -0.60, -0.29]. The reduction in FPG in patients treated with sitagliptin and insulin (with or without metformin) was -55.5 mg/dL compared to -44.8 mg/dL in patients treated with placebo and insulin (with or without metformin), a difference of -10.7 mg/dL [95% CI: -17.2, -4.3]. The incidence of symptomatic hypoglycemia was 25.2% in patients treated with sitagliptin and insulin (with or without metformin) and 36.8% in patients treated with placebo and insulin (with or without metformin). The difference in incidence of hypoglycemia (-11.6%) was statistically significant (p=0.001). The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycemia (9.4 vs. 19.1 %). There was no difference in the incidence of severe hypoglycemia.

TECOS Cardiovascular Safety Study

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a randomized study in 14,671 patients in the intention-to-treat population with an HbA_{1c} of ≥6.5 to 8.0% with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥30 and <50 mL/min/1.73 m^2) or placebo (7,339) added to usual care targeting regional standards for HbA_{1c} and CV risk factors. Patients with an eGFR <30 mL/min/1.73 m^2 were not to be enrolled in the study. The study population included 2,004 patients ≥75 years of age and 3,324 patients with renal impairment (eGFR < 60 mL/min/1.73 m^2).

Over the course of the study, the overall estimated mean (SD) difference in HbA_{1c} between the sitagliptin and placebo groups was 0.29% (0.01), 95% CI (-0.32, -0.27); p<0.001. Patients in the sitagliptin group received fewer antihyperglycemic agents than did those in the placebo group (hazard ratio 0.72; 95% CI, 0.68 to 0.77; p≤0.001) and, among patients not on insulin at study entry, were less likely to start chronic insulin therapy (hazard ratio 0.70; 95% CI, 0.63 to 0.79; p<0.001).

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke; first occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.

After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalization for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes (Table 11).

Table 11: Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	Sitagliptin 100 mg		**Placebo**		**Hazard Ratio (95% CI)**	**p-value[†]**
	N (%)	**Incidence Rate per 100 Patient-**	**N (%)**	**Incidence Rate per 100 Patient-**		

		Years*		Years*		
Analysis in the Per-Protocol Population						
Number of Patients	**7,257**		**7,266**			
Primary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina)	695 (9.6)	3.7	695 (9.6)	3.8	0.98 (0.88 - 1.09)	<0.001
Secondary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke)	609 (8.4)	3.2	602 (8.3)	3.3	0.99 (0.89 - 1.11)	<0.001
Analysis in the Intention-to-Treat Population						
Number of Patients	**7,332**		**7,339**			
Primary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2	0.98 (0.89 - 1.08)	<0.001
Secondary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke)	745 (10.2)	3.6	746 (10.2)	3.6	0.99 (0.89 - 1.10)	<0.001
Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89 - 1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81 - 1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79 - 1.19)	0.760
Hospitalization for unstable angina	116 (1.6)	0.5	129 (1.8)	0.6	0.90 (0.70 - 1.16)	0.419
Death from any cause	547 (7.5)	2.5	537 (7.3)	2.5	1.01 (0.90 - 1.14)	0.875
Hospitalization for heart failure‡	228 (3.1)	1.1	229 (3.1)	1.1	1.00 (0.83 - 1.20)	0.983

* Incidence rate per 100 patient-years is calculated as 100 × (total number of patients with ≥1 event during eligible exposure period per total patient-years of follow-up).
† Based on a Cox model stratified by region. For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard ratio is less than 1.3. For all other endpoints, the p-values correspond to a test of differences in hazard rates.
‡ The analysis of hospitalization for heart failure was adjusted for a history of heart failure at baseline.

Sitagliptin in Pediatric Patients with Type 2 Diabetes and Inadequate Glycemic Control

A 54-week, double-blind study was conducted to evaluate the efficacy and safety of sitagliptin 100 mg once daily in pediatric patients (10 to 17 years of age) with type 2 diabetes who were not on anti-

hyperglycaemic therapy for at least 12 weeks (with HbA_{1c} 6.5% to 10%) or were on a stable dose of insulin for at least 12 weeks (with HbA_{1c} 7% to 10%). Patients were randomized to sitagliptin 100 mg or placebo once daily for 20 weeks.

Mean baseline HbA_{1c} was 7.5%. Treatment with sitagliptin 100 mg did not provide significant improvement in HbA_{1c} at 20 weeks. The reduction in HbA_{1c} in patients treated with sitagliptin (N=95) was 0.0% compared to 0.2% in patients treated with placebo (N=95), a difference of -0.2% (95% CI: -0.7, 0.3).

5.2 Pharmacokinetic properties

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 T_{max}) occurring 1 to 4 hours post-dose. 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 μM•hr, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) 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 [^{14}C]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 [^{14}C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ 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 Impairment

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 impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with ESRD on hemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses.

Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment (eGFR ≥ 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2) and patients with moderate renal impairment (eGFR ≥ 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2), respectively. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Plasma AUC levels of sitagliptin were increased approximately 2-fold in patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2) and approximately 4-fold in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), including patients with ESRD on hemodialysis. Sitagliptin was modestly removed by hemodialysis (13.5% over a 3- to 4-hour hemodialysis session starting 4 hours post-dose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with eGFR < 45 mL/min/1.73 m^2 (see section 4.2).

Hepatic Impairment

In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100 mg dose of sitagliptin. These differences are not considered to be clinically meaningful. No dosage adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment.

There is no clinical experience in patients with severe hepatic impairment (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

The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in pediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18% lower compared to adult patients with type 2

diabetes for a 100 mg dose. This is not considered to be a clinically meaningful difference based on the flat PK/PD relationship between the dose of 50 mg and 100 mg in adults.

No studies with sitagliptin have been performed in pediatric patients < 10 years of age.

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 C_{max} 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 sitagliptin 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.

Metformin: Co-administration of multiple twice-daily doses of metformin with sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

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 C_{max} 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.

5.3 Preclinical safety data
Carcinogenesis, Mutagenesis, Impairment of Fertility
A two-year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of combined liver adenoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results in exposures approximately 60 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 100 mg/day based on AUC comparisons. Liver tumors were not observed at 150 mg/kg, approximately 20 times the human exposure at the MRHD. A two-year carcinogenicity study was conducted in male and female mice given oral doses of sitagliptin of 50, 125, 250, and 500 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 500 mg/kg, approximately 70 times human exposure at the MRHD. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an *in vitro* cytogenetics assay in CHO, an *in vitro* rat hepatocyte DNA alkaline elution assay, and an *in vivo* micronucleus assay.

In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination (approximately 8 weeks total) and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, non-dose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core
Calcium Hydrogen Phosphate Anhydrous
Microcrystalline cellulose
Croscarmellose sodium
Low-Substituted Hydroxypropyl Cellulose
Colloidal Silicon Dioxide
Magnesium stearate

Sodium stearyl fumarate

Coating
Hydroxypropylmethyl cellulose
Hydroxypropylcellulose
Polyethylene glycol 6000
Titanium dioxide
Ferric oxide, yellow
Ferric oxide, red
Ferric oxide, black (only in 100mg strength)
Talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Please refer to outer carton.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
PVDC-Alu blisters, Alu-Alu blisters.
Pack sizes: 7, 10, 14 (2x7), 28 (4x7), 30 (3x10), 42 (6x7), 60 (6x10) tablets.

Not all pack size may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste should be disposed of in accordance with local requirements.

7. MANUFACTURER
Sandoz Private Limited
MIDC, Plot No. 8-A/2 & 8-B
T.T.C. Industrial Area, Kalwe Block,
400708 Navi Mumbai, India

8. DATE OF REVISION OF THE TEXT
Sep 2024