

JANUMET®**(sitagliptin phosphate/metformin HCl)****Film-coated Tablets****I. THERAPEUTIC CLASS***JANUMET*

JANUMET (sitagliptin phosphate/metformin HCl) combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Sitagliptin phosphate

Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). 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. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. This mechanism is unlike the mechanism seen with sulfonylureas; sulfonylureas cause insulin release even when glucose levels are low, which can lead to sulfonylurea-induced hypoglycemia in patients with type 2

diabetes and in normal subjects. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPAR γ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

Metformin hydrochloride

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **PRECAUTIONS**, *Metformin hydrochloride*) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

II. COMPOSITION

Ila. Active Ingredients

JANUMET is available for oral administration as tablets containing 64.25 mg sitagliptin phosphate monohydrate and metformin hydrochloride equivalent to: 50 mg sitagliptin as free base and 500 mg metformin hydrochloride (JANUMET 50 mg/500 mg), 850 mg metformin hydrochloride (JANUMET 50 mg/850 mg) or 1000 mg metformin hydrochloride (JANUMET 50 mg/1000 mg).

III. CLINICAL PHARMACOLOGY

IIIa. Mechanism of Action

JANUMET

JANUMET combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Sitagliptin phosphate

Sitagliptin phosphate is a member of a class of oral antihyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycemic control in patients with type 2 diabetes by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinitropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. 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. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose-dependent. When blood

glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin secretion is enhanced as glucose rises above normal concentrations. GLP-1 does not impair the normal glucagon response to hypoglycemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. This glucose dependent mechanism is unlike the mechanism seen with sulfonylureas where insulin is released even when glucose levels are low, which can lead to hypoglycemia in patients with type 2 diabetes and in normal subjects. In patients with type 2 diabetes with hyperglycemia, these changes in insulin and glucagon levels lead to lower hemoglobin A_{1c} (HbA_{1c}) and lower fasting and postprandial glucose concentrations. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations.

Metformin hydrochloride

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **PRECAUTIONS**, *Metformin hydrochloride*) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

IIIb. Pharmacokinetics

JANUMET

The results of a definitive bioequivalence study in healthy subjects demonstrated that the JANUMET (sitagliptin/metformin hydrochloride) 50 mg/500 mg and 50 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of sitagliptin phosphate (JANUVIA™) and metformin hydrochloride as individual tablets.

Because bioequivalence is demonstrated at the lowest and highest combination tablet dose strengths available, bioequivalence is conferred to the (sitagliptin/metformin) 50 mg/850 mg fixed dose combination (FDC) tablet.*

IIIb-1. Absorption

Sitagliptin phosphate

The absolute bioavailability of sitagliptin is approximately 87%. Coadministration of a high-fat meal with sitagliptin phosphate had no effect on the pharmacokinetics of sitagliptin.

Metformin hydrochloride

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alternation in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a

40% lower mean peak plasma concentration ($C_{\max}$), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration ($T_{\max}$) following administration of a single 850-mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

IIIb-2. Distribution

Sitagliptin phosphate

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 hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

IIIb-3. Metabolism

Sitagliptin phosphate

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine.

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 hydrochloride

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) nor biliary excretion.

IIIb-4. Elimination

Sitagliptin phosphate

Following administration of an oral [¹⁴C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ 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.

Metformin hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. 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.

IIIb-5. Characteristics in Patients

Type 2 Diabetes

Sitagliptin phosphate

The pharmacokinetics of sitagliptin in patients with type 2 diabetes are generally similar to those in healthy subjects.

Metformin hydrochloride

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.

Renal Impairment

Sitagliptin phosphate

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to <45 mL/min/1.73 m², and an approximately 4-fold increase was observed in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²) including patients with end-stage renal disease (ESRD) on hemodialysis, as compared to subjects with normal renal function.

Metformin hydrochloride

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

Hepatic Impairment

Sitagliptin phosphate

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 phosphate. These differences are not considered to be clinically meaningful.

There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score >9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

Metformin hydrochloride

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

Gender

Sitagliptin phosphate

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.

Metformin hydrochloride

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

Elderly

Sitagliptin phosphate

Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Metformin hydrochloride

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 C_{max} 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 (see **GLUCOPHAGE**¹ prescribing information: **CLINICAL PHARMACOLOGY**, Special Populations, Geriatrics).

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

Sitagliptin phosphate

Race 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, including subjects of white, Hispanic, black, Asian, and other racial groups.

Metformin hydrochloride

¹ **GLUCOPHAGE**® is a registered trademark of Merck Sante S.A.S, an associate of Merck KGaA of Darmstadt, Germany. Licensed to Bristol-Meyers Squibb Company.

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

Body Mass Index (BMI)

Sitagliptin phosphate

Body mass index (BMI) 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.

IIIc. Pharmacodynamics

Sitagliptin phosphate

General

In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24-hour period, resulting in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose excursion following an oral glucose load or a meal.

In Phase III clinical studies of 18- and 24-week duration, treatment with sitagliptin 100 mg daily in patients with type 2 diabetes significantly improved beta cell function, as assessed by several markers, including HOMA- β (Homeostasis Model Assessment- β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In Phase II studies, sitagliptin 50 mg twice daily provided similar glycemic efficacy compared to sitagliptin 100 mg once daily.

In a randomized, placebo-controlled, double-blind, double-dummy, four-period crossover two-day study in healthy adult subjects, the effects on post-meal plasma concentrations of active and total GLP-1 and glucose after coadministration of sitagliptin and metformin were compared with those after administration of sitagliptin alone, metformin alone or placebo, each administered for two days. The incremental 4-hour post-meal weighted mean active GLP-1 concentrations were increased approximately 2-fold after either administration of sitagliptin alone or metformin alone compared with placebo. The effect on active GLP-1 concentrations after coadministration of sitagliptin and metformin were additive, with active GLP-1 concentrations increased by approximately 4-fold compared with placebo. Sitagliptin alone increased only active GLP-1 concentrations, reflecting inhibition of DPP-4, whereas metformin alone increased active and total GLP-1 concentrations to a similar extent. These data are consistent with different mechanisms for the increase in active GLP-1 concentrations. Results from the study also demonstrated that sitagliptin, but not metformin, enhances active GIP concentrations.

In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia, suggesting that the insulinotropic and glucagon suppressive actions of the drug are glucose dependent.

Effects on blood pressure

In a randomized, placebo-controlled crossover study in hypertensive patients on one or more anti-hypertensive drugs (including angiotensin-converting enzyme inhibitors, angiotensin-II antagonists, calcium-channel blockers, beta-blockers and diuretics), coadministration with sitagliptin was generally well tolerated. In these patients, sitagliptin had a modest blood pressure lowering effect; 100 mg per day of sitagliptin reduced 24-hour mean ambulatory systolic blood pressure by approximately 2 mmHg, as compared to placebo. Reductions have not been observed in subjects with normal blood pressure.

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 small increase was 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.

III.d. Clinical Studies

Clinical studies of the coadministration of sitagliptin and metformin demonstrated significant improvements in glycemic control in adult patients with type 2 diabetes. None of the clinical efficacy studies in adults described below was conducted with JANUMET tablets; however, bioequivalence of JANUMET tablets with coadministered sitagliptin and metformin hydrochloride tablets was demonstrated.

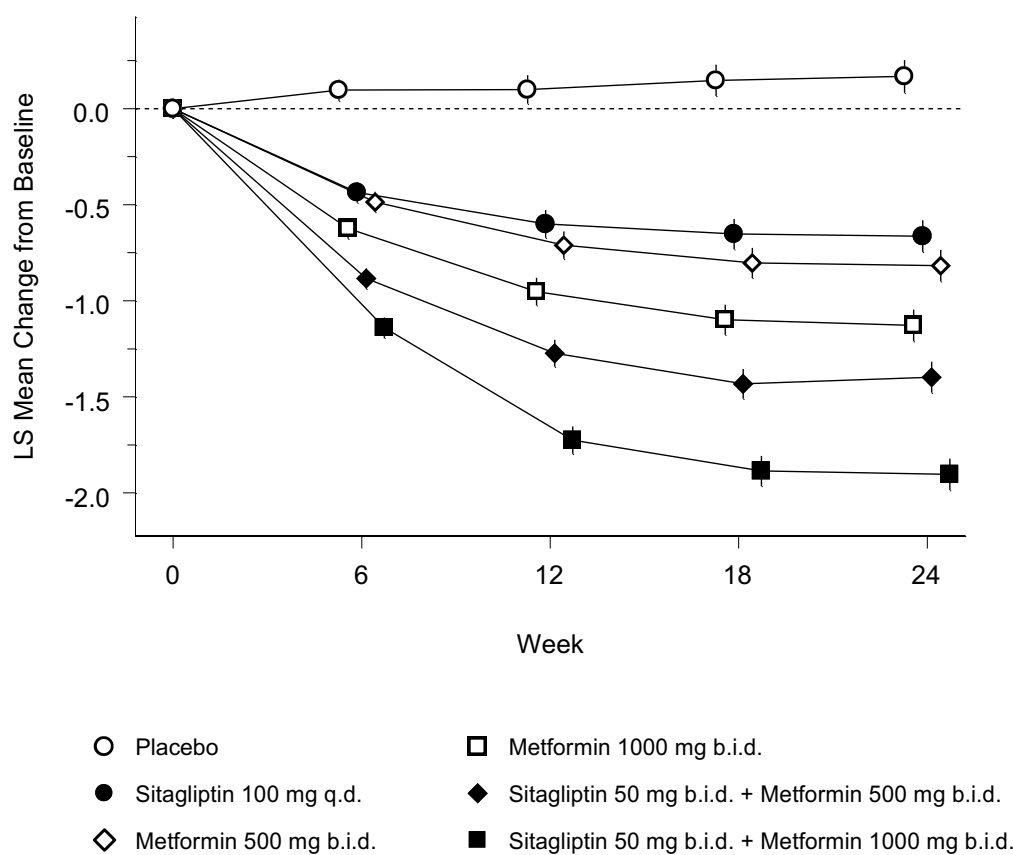
Sitagliptin and Metformin as Initial Therapy in Patients with Type 2 Diabetes

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 safety and efficacy of initial therapy with the

combination of sitagliptin and metformin. 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.

Initial therapy with the combination of sitagliptin and metformin provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to sitagliptin alone ($p < 0.001$; Table 3, Figure 1). An improvement in FPG, with near maximal FPG reduction, was achieved by the 3-week time point (the first time point assessed after initiation of therapy) and sustained throughout the 24-week study. Measures of beta cell function, HOMA- β and the proinsulin to insulin ratio also showed greater improvement with the coadministration of sitagliptin and metformin compared with either monotherapy alone. 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. Mean reductions from baseline in HbA_{1c} compared with placebo were generally greater for patients with higher baseline HbA_{1c} values. The improvement in HbA_{1c} was generally consistent across subgroups defined by gender, age, race, or baseline BMI. Mean reductions from baseline in HbA_{1c} for patients not on an antihyperglycemic agent at study entry were: sitagliptin 100 mg once daily, -1.06%; metformin 500 mg bid, -1.09%; metformin 1000 mg bid, -1.24%; sitagliptin 50 mg bid with metformin 500 mg bid, -1.59%; and sitagliptin 50 mg bid with metformin 1000 mg bid, -1.94%; and for patients receiving placebo, -0.17%.

Figure 1: Mean Change from Baseline for HbA_{1c} 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.

Table 3
Glycemic Parameters and Body Weight at Final Visit (24-Week Study)
for Sitagliptin and Metformin, Alone and in Combination as Initial Therapy†

	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 mg b.i.d.	Sitagliptin 50 mg b.i.d. + Metformin 500 mg b.i.d.	Metformin 1000 mg b.i.d.	Sitagliptin 50 mg b.i.d. + Metformin 1000 mg b.i.d.
HbA_{1c} (%)	N = 165	N = 175	N = 178	N = 183	N = 177	N = 178
Baseline (mean)	8.68	8.87	8.90	8.79	8.68	8.76
Change from baseline (adjusted mean [‡])	0.17	-0.66	-0.82	-1.40	-1.13	-1.90
Difference from placebo (adjusted mean [‡])	-	-0.83 [§]	-0.99 [§]	-1.57 [§]	-1.30 [§]	-2.07 [§]
Patients (%) achieving HbA _{1c} <7%	15 (9.1)	35 (20.0)	41 (23.0)	79 (43.2)	68 (38.4)	118 (66.3)
FPG (mg/dL)	N = 169	N = 178	N = 179	N = 183	N = 179	N = 180
Baseline (mean)	196.3	201.4	205.2	203.9	197.0	196.7
Change from baseline (adjusted mean [‡])	5.8	-17.5	-27.3	-47.1	-29.3	-63.9
Difference from placebo (adjusted mean [‡])	-	-23.3 [§]	-33.1 [§]	-52.9 [§]	-35.1 [§]	-69.7 [§]

2-hour PPG (mg/dL)	N = 129	N = 136	N = 141	N = 147	N = 138	N = 152
Baseline (mean)	276.8	285.4	292.7	291.8	283.4	286.9
Change from baseline (adjusted mean [†])	0.3	-51.9	-53.4	-92.5	-78.0	-116.6
Difference from placebo (adjusted mean [†])		-52.2 [§]	-53.7 [§]	-92.8 [§]	-78.3 [§]	-116.9 [§]
Body Weight (kg)	N = 167	N = 175	N = 179	N = 184	N = 175	N = 178
Baseline (mean)	90.1	85.9	88.1	90.0	89.4	88.2
Change from baseline (adjusted mean [†])	-0.9	0.0	-0.9	-0.6	-1.1	-1.3
Difference from placebo (adjusted mean [†])		0.9 [¶]	0.1 [#]	0.4 [#]	-0.1 [#]	-0.3 [#]

[†] All Patients Treated Population (an intention-to-treat analysis).

[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

[§] p<0.001 compared to placebo.

^{||} All Patients as Treated (APaT) population, excluding data following glycemic rescue therapy.

[¶] p=0.005 compared to placebo.

[#]Not statistically significant (p≥ 0.05) compared to placebo.

In addition, this study included patients (N=117) with more severe hyperglycemia (HbA_{1c} >11% or blood glucose >280 mg/dL) who were treated with open-label sitagliptin at 50 mg and metformin at 1000 mg twice daily. In this group of patients, the baseline HbA_{1c} value was 11.15%, FPG was 314.4 mg/dL, and 2-hour PPG was 441.0 mg/dL. After 24 weeks, decreases from baseline of -2.94 % for HbA_{1c}, -126.7 mg/dL for FPG,

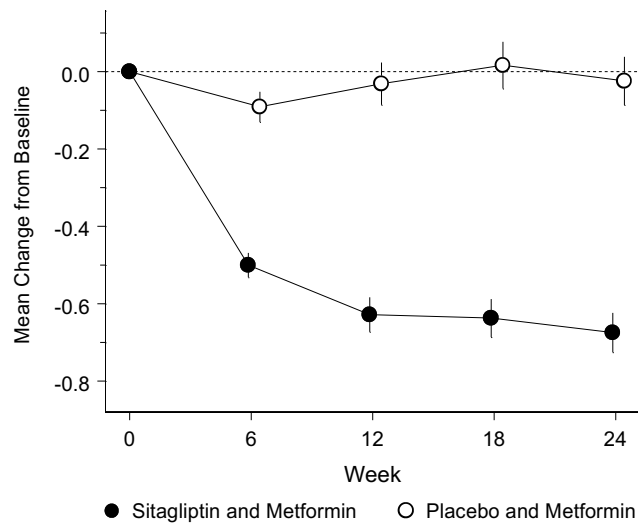
and -207.9 mg/dL for 2-hour PPG were observed. In this open-label cohort, a modest increase in body weight of 1.3 kg was observed at 24 weeks.

Sitagliptin Add-on Therapy in Patients Inadequately Controlled on Metformin Alone:

The combination of sitagliptin and metformin has been evaluated for safety and efficacy in two double-blind, placebo-controlled clinical studies in patients with type 2 diabetes mellitus. In both studies, patients with inadequate glycemic control on stable doses of metformin $\geq$ 1500 mg were randomized to receive either sitagliptin 100 mg per day or placebo in addition to ongoing treatment with metformin.

In one study, 701 patients received 100 mg of sitagliptin or placebo once daily for 24 weeks. The addition of sitagliptin to ongoing metformin treatment provided significant improvements compared with the addition of placebo to ongoing metformin treatment in HbA_{1c} (-0.65%), FPG (-25.4 mg/dL), and 2-hour PPG (-50.6 mg/dL) (see Figure 2 and Table 4). This improvement in HbA_{1c} compared to placebo was not affected by baseline HbA_{1c} value, prior antihyperglycemic therapy, gender, age, baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome, or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA- β). Compared to patients taking placebo, patients taking sitagliptin demonstrated slight decreases in total cholesterol, non-HDL cholesterol and triglycerides. A similar decrease in body weight was observed for both treatment groups.

Figure 2: Mean Change from Baseline for HbA_{1c} over 24 Weeks with Sitagliptin 100-mg Total Daily Dose and Metformin or Placebo and Metformin in Patients with Type 2 Diabetes† ‡



† Patients with inadequate glycemic control on metformin monotherapy.

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

**Table 4: Glycemic Parameters and Body Weight at Final Visit (24-Week Study)
Sitagliptin as Add-on Therapy in Patients with Inadequate Glycemic Control on
Metformin †**

	Sitagliptin 100 mg q.d. + Metformin	Placebo + Metformin
HbA_{1c} (%)	N = 453	N = 224
Baseline (mean)	7.96	8.03
Change from baseline (adjusted mean [‡])	-0.67	-0.02
Difference from placebo + metformin (adjusted mean [‡])	-0.65 [§]	
Patients (%) achieving HbA _{1c} <7%	213 (47.0)	41 (18.3)
FPG (mg/dL)	N = 454	N = 226
Baseline (mean)	170.0	173.5
Change from baseline (adjusted mean [‡])	-16.9	8.5
Difference from placebo + metformin (adjusted mean [‡])	-25.4 [§]	
2-hour PPG (mg/dL)	N = 387	N = 182
Baseline (mean)	274.5	272.4
Change from baseline (adjusted mean [‡])	-62.0	-11.4
Difference from placebo + metformin (adjusted mean [‡])	-50.6 [§]	
Body Weight (kg) 	N = 399	N = 169
Baseline (mean)	86.9	87.6

Change from baseline (adjusted mean [‡])	-0.7	-0.6
Difference from placebo + metformin (adjusted mean [‡])	-0.1 [¶]	

[†] All Patients Treated Population (an intention-to-treat analysis).

[‡] Least squares means adjusted for prior antihyperglycemic therapy and baseline value.

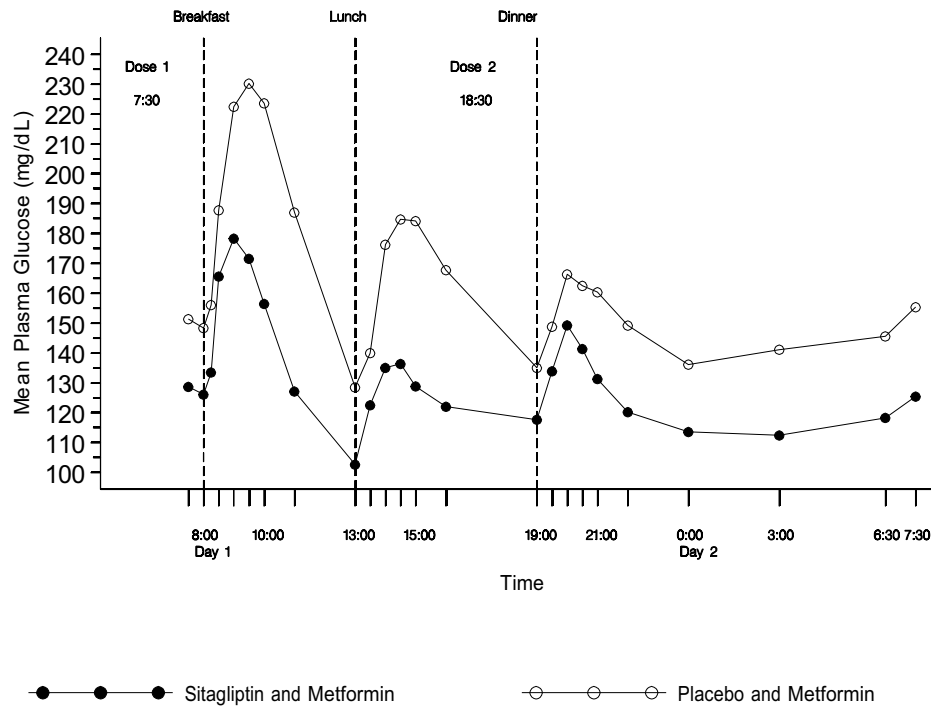
[§] p<0.001 compared to placebo + metformin.

[¶] All Patients as Treated (APaT) population, excluding data following glycemic rescue therapy.

^{¶¶} Not statistically significant (p≥ 0.05) compared to placebo + metformin.

In a separate study, 24-hour plasma glucose values were assessed. Twenty-eight patients received either 50 mg sitagliptin or placebo twice daily for 4 weeks in addition to their twice daily metformin regimen. Following 4 weeks of treatment, the difference in glucose lowering efficacy was assessed as a 24-hour weighted mean glucose (WMG) based upon collection of multiple blood samples, including those obtained before and after meals as well as overnight. Sitagliptin 50 mg coadministered twice daily with metformin significantly lowered the 24-hour WMG (-32.8 mg/dL) compared to placebo coadministered with metformin. In addition, sitagliptin administered with metformin, compared with placebo administered with metformin, substantially lowered fasting glucose concentrations and demonstrated smaller glucose excursions after all three meals (see Figure 3). In patient-collected glucose measurements, treatment with sitagliptin administered with metformin also provided significant reductions compared to placebo administered with metformin in mean fasting plasma glucose (-20.3 mg/dL), 7-point glucose average (-28.0 mg/dL), and 2 hour post-glucose concentrations (-36.6 mg/dL).

Figure 3: 24-hour Plasma Glucose Profile after 4-Week Treatment with Sitagliptin 50-mg BID and Metformin or Placebo and Metformin in Patients with Type 2 Diabetes†



† Patients with inadequate glycemic control on metformin monotherapy.

Sitagliptin Add-on Therapy in Patients Inadequately Controlled on the Combination of Metformin 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 100 mg once daily compared to placebo in combination with glimepiride (alone or in combination with metformin). In this study, 220 patients were on the combination of

glimepiride (≥ 4 mg per day) and metformin (≥ 1500 mg per day); the results of the glycemic endpoints, including HbA_{1c} and FPG, are described below.

The combination of sitagliptin, glimepiride, and metformin provided significant reduction from baseline in HbA_{1c} (-0.89%) and FPG (-20.7 mg/dL) compared to placebo (see Table 5). Mean reductions from baseline in HbA_{1c} compared with placebo were generally greater for patients with higher baseline HbA_{1c} values. Patients treated with sitagliptin had a modest increase in body weight compared to those given placebo.

Table 5
Glycemic Parameters and Body Weight at Final Visit (24-Week Study)
for Sitagliptin as Add-on Combination Therapy with Glimepiride and Metformin†

	Sitagliptin 100 mg + Glimepiride + Metformin	Placebo + Glimepiride + Metformin
HbA_{1c} (%)	N = 115	N = 105
Baseline (mean)	8.27	8.28
Change from baseline (adjusted mean [‡])	-0.59	0.30
Difference from placebo (adjusted mean [‡])	-0.89 [§]	
Patients (%) achieving HbA _{1c} <7%	26 (22.6)	1 (1.0)
FPG (mg/dL)	N = 115	N = 109
Baseline (mean)	179.3	178.9
Change from baseline (adjusted mean [‡])	-7.8	12.9
Difference from placebo (adjusted mean [‡])	-20.7 [§]	
Body Weight (kg)	N = 102	N = 74

Baseline (mean)	86.5	84.6
Change from baseline (adjusted mean [‡])	0.4	-0.7
Difference from placebo (adjusted mean [‡])	1.1 ^{† †}	

† All Patients Treated Population (an intention-to-treat analysis).

‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

§ p<0.001 compared to placebo.

|| All Patients as Treated (APaT) population, excluding data following glycemic rescue therapy.

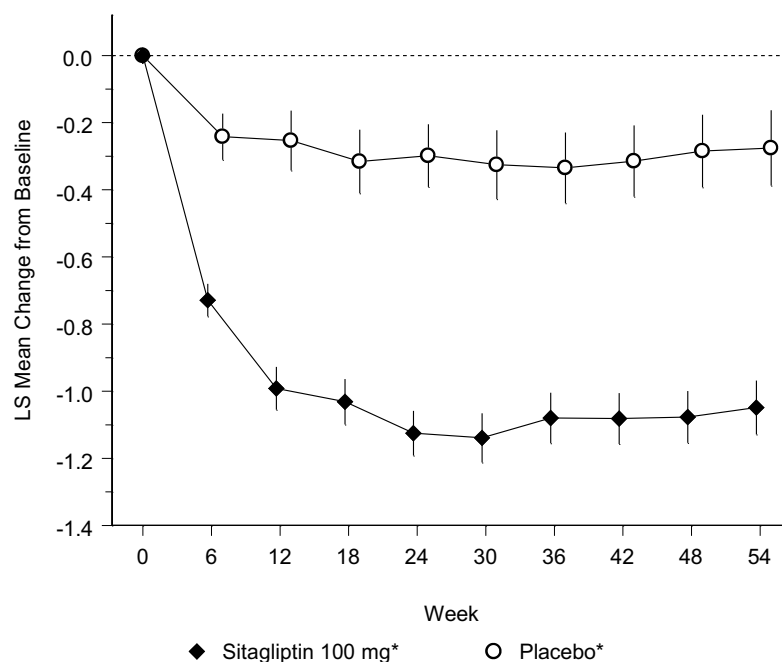
† † p=0.007 compared to placebo.

Sitagliptin Add-on Therapy in Patients Inadequately Controlled on the Combination of Metformin and Rosiglitazone:

A total of 262 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 and rosiglitazone. Patients with inadequate glycemic control on a stable regimen of metformin (≥ 1500 mg per day) and rosiglitazone (≥ 4 mg per day) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Glycemic parameters were evaluated at the primary time point of Week 18 and at Week 54.

In combination with metformin and rosiglitazone, sitagliptin provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo with metformin and rosiglitazone (Table 6, Figure 4) at Week 18, with improvements sustained through the end of the study. Lipid effects were generally neutral. There was no significant difference between sitagliptin and placebo in body weight change.

Figure 4: Mean Change from Baseline for HbA_{1c} (%) Over 54 Weeks in a Study of Sitagliptin as Add-on therapy in Patients Inadequately Controlled on Metformin and Rosiglitazone†



† All Patients Treated Population; Least squares means adjusted for prior antihyperglycemic therapy and baseline value (error bars = standard error).

*Added to ongoing therapy with metformin and rosiglitazone.

Table 6

**Glycemic Parameters and Body Weight at Week 18 and Week 54 (Final Visit)
for Sitagliptin in Add-on Combination Therapy with Metformin and Rosiglitazone †**

	Week 18		Week 54	
	Sitagliptin 100 mg + Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone	Sitagliptin 100 mg + Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone
HbA_{1c} (%)	N = 168	N = 88	N = 168	N = 88
Baseline (mean)	8.81	8.73	8.81	8.73
Change from baseline (adjusted mean [‡])	-1.03	-0.31	-1.05	-0.28
Difference from placebo + rosiglitazone + metformin (adjusted mean [‡])	-0.72 [§]		-0.77 [§]	
Patients (%) achieving A1C <7%	37 (22%)	8 (9%)	44 (26%)	12 (14%)
FPG (mg/dL)	N = 169	N = 89	N = 169	N = 89
Baseline (mean)	182.1	183.5	182.1	183.5
Change from baseline (adjusted mean [‡])	-30.7	-11.7	-28.0	-10.7
Difference from placebo + rosiglitazone + metformin (adjusted mean [‡])	-19.0 [§]		-17.4 [§]	
2-hour PPG (mg/dL)	N = 142	N = 75	N = 147	N = 77
Baseline (mean)	257.8	249.5	256.6	247.7
Change from baseline	-59.9	-22.0	-50.7	-16.6

(adjusted mean [‡])				
Difference from placebo + rosiglitazone + metformin (adjusted mean [‡])	-37.9 [§]		-34.1 [§]	
Body Weight (kg)	N = 157	N = 79	N = 115	N = 40
Baseline (mean)	82.1	87.0	82.0	85.6
Change from baseline (adjusted mean [‡])	0.5	0.2	1.9	1.3
Difference from placebo + metformin + rosiglitazone (adjusted mean [‡])	0.3 [¶]		0.6 [¶]	

† All patients treated population (an intention-to-treat analysis).

‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

§ p<0.001 compared to placebo + metformin + rosiglitazone.

|| All Patients as Treated (APaT) population, excluding data following glycemic rescue therapy.

¶ Not statistically significant (p≥ 0.05) compared to placebo + metformin + rosiglitazone.

Sitagliptin Add-on Therapy in Patients Inadequately Controlled on the Combination of Metformin 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 100 mg once daily in combination with a stable dose of insulin. Approximately 75% of patients were also taking metformin. Patients on pre-mixed, long-acting or intermediate acting insulin (with or without metformin) were randomized to the addition of either 100 mg of sitagliptin or placebo. Glycemic endpoints measured included HbA_{1c}, FPG and 2-hour PPG.

The combination of sitagliptin, metformin and insulin provided significant improvements in HbA_{1c}, FPG and 2-hour PPG compared to placebo (Table 7). The improvement in HbA_{1c} compared to placebo was generally consistent across subgroups defined by gender, age, race, baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome, or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA- β). There was no meaningful change from baseline in body weight in either group.

Table 7
Glycemic Parameters and Body Weight at Final Visit (24-Week Study)
for Sitagliptin as Add-on Combination Therapy with Metformin and a Stable Dose of
Insulin†

	Sitagliptin 100 mg + Insulin + Metformin	Placebo + Insulin + Metformin
HbA_{1c} (%)	N = 223	N = 229
Baseline (mean)	8.73	8.60
Change from baseline (adjusted mean [‡])	-0.66	-0.13
Difference from placebo (adjusted mean [‡] , §)	-0.53	
Patients (%) achieving HbA _{1c} <7%	32 (14.3)	12 (5.2)
FPG (mg/dL)	N = 225	N = 229
Baseline (mean)	173.5	175.6
Change from baseline (adjusted mean [‡])	-22.2	-3.9
Difference from placebo (adjusted mean [‡])	-18.3	
2-hour PPG (mg/dL)	N = 182	N = 189
Baseline (mean)	280.7	280.6
Change from baseline (adjusted mean [‡])	-39.0	1.5
Difference from placebo (adjusted mean [‡])	-40.4	
Body Weight (kg) ¶	N = 201	N = 200
Baseline (mean)	87.9	88.0

Change from baseline (adjusted mean [†])	-0.1	0.0
Difference from placebo (adjusted mean [‡])	-0.1 [#]	

[†] All Patients Treated Population (an intention-to-treat analysis).

[‡] Least squares mean adjusted for insulin use at Visit 1 (premixed 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.

[¶] All Patients as Treated (APaT) population, excluding data following glycemic rescue therapy.

[#] Not statistically significant ($p \geq 0.05$) 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. Among patients taking metformin, baseline HbA_{1c} was 8.70% 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.

Among patients taking metformin, at Week 24, the increase in daily insulin dose was 21% smaller in patients treated with sitagliptin (19 IU/day, N=285) than in patients treated with placebo (24 IU/day, N=283). The difference in insulin dose (-5 IU/day) was statistically significant ($p=0.007$). The reduction in HbA_{1c} for patients treated with sitagliptin, metformin, and insulin was -1.35% compared to -0.90% for patients treated with placebo, metformin, and insulin, a difference of -0.45% [95% CI: -0.62, -0.29]. The reduction in FPG for patients treated with sitagliptin, metformin, and insulin was -54.8 mg/dL compared to -43.0 mg/dL for patients treated with placebo, metformin, and

insulin, a difference of -11.8 mg/dL [95% CI: -18.7, -4.9]. The incidence of hypoglycemia was 24.9% for patients treated with sitagliptin, metformin, and insulin and 37.8% for patients treated with placebo, metformin and insulin. The difference in incidence of hypoglycemia (-12.9%) was statistically significant ($p < 0.001$).

Active (Glipizide)-Controlled Study in Combination with Metformin

Long-term maintenance of effect was evaluated in a 52-week, double-blind, glipizide-controlled trial in patients with type 2 diabetes and inadequate glycemic control on metformin monotherapy at ≥ 1500 mg/day. In this study, patients were randomized to the addition of either sitagliptin 100 mg daily ($N = 588$) or glipizide ($N = 584$) for 52 weeks. Patients receiving glipizide were given an initial dosage of 5 mg/day and then electively titrated by the investigator to a target FPG of <110 mg/dL, without significant hypoglycemia, over the next 18 weeks. A maximum dosage of 20 mg/day was allowed to optimize glycemic control. Thereafter, the glipizide dose was to have been kept constant. The mean dose of glipizide after the titration period was 10.3 mg.

Both treatments resulted in a statistically significant improvement in glycemic control from baseline. After 52 weeks, the reduction from baseline in HbA_{1c} was 0.67% for sitagliptin 100 mg daily and 0.67% for glipizide, confirming comparable efficacy of the two agents. The reduction in FPG was 10.0 mg/dL for sitagliptin and 7.5 mg/dL for glipizide. In a post-hoc analysis, patients with higher baseline HbA_{1c} ($\geq 9\%$) in both groups had greater reductions from baseline in HbA_{1c} (sitagliptin, -1.68%; glipizide, -1.76%). In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with sitagliptin and deteriorated with glipizide treatment. The incidence of hypoglycemia in the sitagliptin group (4.9%) was significantly 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).

Metformin hydrochloride

The prospective randomized (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), $p=0.0023$, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), $p=0.0034$.
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, $p=0.017$.
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years ($p=0.011$), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1000 patient-years ($p=0.021$).
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years ($p=0.01$).

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 m²) 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 m² 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 m²).

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); $p < 0.001$.

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal 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 8).

Table 8
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-Years*	N (%)	Incidence Rate per 100 Patient-Years*		
Analysis in the Intention-to-Treat Population						
Number of Patients	7,332		7,339		0.98 (0.89–1.08)	<0.001
Primary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2		
Secondary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, or nonfatal 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

					1.19)	
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 $100 \times (\text{total number of patients with } \geq 1 \text{ event during eligible exposure period per total patient-years of follow-up})$.

† 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 Add-on Therapy in Pediatric Patients Inadequately Controlled on Metformin with or without Insulin:

A combined total of 220 pediatric patients aged 10 to 17 years with type 2 diabetes and inadequate glycemic control on metformin with or without insulin participated in two randomized, double-blind, placebo-controlled, parallel-group studies over 54 weeks. The addition of sitagliptin 100 mg (administered as JANUMET or JANUMET XR) was compared to the addition of placebo to metformin or metformin XR.

Superiority of HbA_{1c} reduction was demonstrated for JANUMET/JANUMET XR over metformin at Week 20 in the pooled analysis of these two studies. The reduction in

HbA_{1c} in patients treated with JANUMET/JANUMET XR (N=107) was -0.6% compared to -0.1% in patients treated with metformin (N=113), a difference of -0.5% (95% CI: -0.9, -0.1). However, results from the individual studies were inconsistent, and efficacy for JANUMET/JANUMET XR over metformin was not observed at Week 54. These results do not support use of JANUMET or JANUMET XR in pediatric subjects (10 to 17 years old) with type 2 diabetes.

IV. INDICATIONS

JANUMET is indicated as initial therapy in patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise do not provide adequate glycemic control.

JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus inadequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

JANUMET is indicated as part of triple combination therapy with a sulfonylurea as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled with any two of the three agents: metformin, sitagliptin, or a sulfonylurea.

JANUMET is indicated as triple combination therapy with a PPAR γ agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPAR γ agonist.

JANUMET is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in patients when stable dosage of insulin and metformin alone do not provide adequate glycemic control.

V. DOSAGE AND ADMINISTRATION

General

The dosage of antihyperglycaemic therapy with JANUMET should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100mg sitagliptin. Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

JANUMET should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects associated with metformin.

The starting dose of JANUMET should be based on the patient's current regimen. JANUMET should be given twice daily with meals.

Patients inadequately controlled with diet and exercise alone:

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient with type 2 diabetes mellitus inadequately controlled with diet and exercise alone, the recommended starting dose is 50mg sitagliptin/500mg metformin hydrochloride twice daily. Patients with inadequate glycaemic control on this dose can be titrated up to 50mg sitagliptin/ 1000mg metformin hydrochloride twice daily.

Patients inadequately controlled on metformin monotherapy.

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient inadequately controlled on metformin alone, the recommended starting dose of JANUMET should provide sitagliptin dosed as 50mg twice daily (100mg total daily dose), and the dose of metformin already being taken.

Patients inadequately controlled on sitagliptin monotherapy.

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient inadequately controlled on sitagliptin alone, the recommended starting dose of JANUMET is 50mg sitagliptin/ 500mg metformin hydrochloride twice daily. Patients with inadequate control on this dose can be titrated up to 50mg sitagliptin/ 1000mg metformin hydrochloride twice daily. Patients taking sitagliptin monotherapy dose-adjusted for renal impairment should not be switched to JANUMET.

Patients switching from coadministration of sitagliptin and metformin:

For patients switching from sitagliptin coadministered with metformin, JANUMET may be initiated at the dose of sitagliptin and metformin already being taken.

Patients inadequately controlled on dual combination therapy with any two of the following three antihyperglycaemic agents: sitagliptin, metformin or a sulfonylurea:

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate in this setting, the usual starting dose of JANUMET should provide sitagliptin dosed as 50mg twice daily (100mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycaemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effect associated with metformin should be considered. Patients currently on or initiating a sulfonylurea may require lower sulfonylurea doses to reduce the risk of hypoglycemia.

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a PPAR γ agonist

The dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.

For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin

The dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When JANUMET is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycemia (see **PRECAUTIONS**).

No studies have been performed specifically examining the safety and efficacy of JANUMET in patients previously treated with other oral antihyperglycaemia agents and switched to JANUMET. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycaemic control can occur.

Renal impairment

An eGFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with eGFR < 60 mL/min/1.73m².

If no adequate strength of JANUMET is available, individual monocomponents should be used instead of the fixed dose combination.

eGFR mL/min	Metformin	Sitagliptin
60-89	Maximum daily dose is 3000mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 100mg.
45-59	Maximum daily dose is 2000mg.	Maximum daily dose is 100mg.

	The starting dose is at most half of the maximum dose.	
30-44	Maximum daily dose is 1000mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 50mg.
< 30	Metformin is contraindicated.	Maximum daily dose is 25mg.

VI. CONTRAINDICATIONS

JANUMET (*sitagliptin phosphate/metformin HCl*) is contraindicated in patients with:

1. Severe renal impairment (eGFR < 30 mL/min/1.73 m²) (see PRECAUTIONS, Monitoring of renal function).
2. Known hypersensitivity to sitagliptin phosphate, metformin hydrochloride or any other component of JANUMET (see PRECAUTIONS, *Sitagliptin phosphate, Hypersensitivity Reactions* and SIDE EFFECTS, *Postmarketing Experience*).
3. Acute or chronic metabolic acidosis, including lactic acidosis, diabetic ketoacidosis, with or without coma.

JANUMET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see PRECAUTIONS; *Metformin hydrochloride*).

VII. PRECAUTIONS

JANUMET

JANUMET should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Pancreatitis: There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis (see **SIDE EFFECTS**), in patients taking sitagliptin. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin. If pancreatitis is suspected, JANUMET and other potentially suspect medicinal products should be discontinued.

Monitoring of renal function: Metformin and sitagliptin are known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. JANUMET is contraindicated in severe renal impairment, patients with an eGFR < 30 mL/min/1.73 m² (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS** and **PRECAUTIONS**, *Metformin hydrochloride, Lactic acidosis*).

Before initiation of therapy with JANUMET and at least annually thereafter, renal function should be assessed. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and JANUMET discontinued if evidence of renal impairment is present.

Hypoglycemia in Combination with a Sulfonylurea or with Insulin : As is typical with other antihyperglycemic agents, hypoglycemia has been observed when sitagliptin and metformin were used in combination with insulin or a sulfonylurea (see **SIDE EFFECTS**). Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia, a lower dose of sulfonylurea or insulin may be considered (see **DOSAGE AND ADMINISTRATION**).

Sitagliptin phosphate

Hypoglycemia in Combination with a Sulfonylurea or with Insulin: In clinical trials of sitagliptin as monotherapy and as part of combination therapy with agents not known to cause hypoglycemia (i.e., metformin or a PPAR γ agonist (thiazolidinedione), rates of hypoglycemia reported with sitagliptin were similar to rates in patients taking placebo. As typical with other antihyperglycemic agents, hypoglycemia has been observed when sitagliptin was used in combination with insulin or a sulfonylurea (see **SIDE EFFECTS**). Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia, a lower dose of sulfonylurea or insulin may be considered (see **DOSAGE AND ADMINISTRATION**).

Hypersensitivity Reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUMET. 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 JANUMET, assess for other potential causes for the event, and institute alternative treatment for diabetes. (See **CONTRAINDICATIONS** and **SIDE EFFECTS**, *Postmarketing Experience*.)

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 JANUMET. If bullous pemphigoid is suspected, JANUMET 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.

Metformin hydrochloride

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET (*sitagliptin phosphate/metformin HCl*); when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 $\mu\text{g/mL}$ are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications (see **DOSAGE AND ADMINISTRATION**, *Recommendations for use in renal impairment*). Patients with

congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function (see **USE IN THE ELDERLY**, *Metformin hydrochloride*). In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug-related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see **CONTRAINDICATIONS**).

Hypoglycemia: Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β -adrenergic blocking drugs.

Use of concomitant medications that may affect renal function or metformin disposition: Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **DRUG INTERACTIONS**, *Metformin hydrochloride*), should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see **CONTRAINDICATIONS**). Therefore, in patients with an eGFR $\geq$ 30 to <60 mL/min/1.73 m², in patients with a history of hepatic impairment, alcoholism, or heart failure, or in patients who will be administered intra-arterial iodinated contrast, JANUMET should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be acceptable (see **DOSAGE AND ADMINISTRATION**).

Hypoxic states: Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on JANUMET therapy, the drug should be promptly discontinued.

Surgical procedures: Use of JANUMET should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as acceptable (see **DOSAGE AND ADMINISTRATION**).

Alcohol intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving JANUMET.

Impaired hepatic function: Since impaired hepatic function has been associated with some cases of lactic acidosis, JANUMET should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B₁₂ levels:

Metformin may reduce Vitamin B₁₂ serum levels. The risk of low Vitamin B₁₂ levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause Vitamin B₁₂ deficiency. In case of suspicion of Vitamin B₁₂ deficiency (such as anemia or neuropathy), Vitamin B₁₂ serum levels should be monitored. Periodic Vitamin B₁₂ monitoring could be necessary in patients with risk factors for Vitamin B₁₂ deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for Vitamin B₁₂ deficiency provided in line with current clinical guidelines.

Change in clinical status of patients with previously controlled type 2 diabetes: A patient with type 2 diabetes previously well controlled on JANUMET who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, JANUMET must be stopped immediately and other appropriate corrective measures initiated.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold JANUMET and temporarily administer insulin. JANUMET may be reinstituted after the acute episode is resolved.

VIII. PREGNANCY

JANUMET

There are no adequate and well-controlled studies in pregnant women with JANUMET or its individual components; therefore, the safety of JANUMET in pregnant women is not known. JANUMET, like other oral antihyperglycemic agents, is not recommended for use in pregnancy.

No animal studies have been conducted with the combined products in JANUMET to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

Sitagliptin phosphate

Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg or in rabbits given up to 125 mg/kg during organogenesis (up to 32 and 22 times, respectively, the human exposure based on the recommended daily adult human dose of 100 mg/day). In rats, a slight increase in the incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) was observed at oral doses of 1000 mg/kg/day (approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Slight decreases in mean preweaning body weights of both sexes and postweaning body weight gains of males were observed in the offspring of rats given oral dose of 1000 mg/kg/day. However, animal reproduction studies are not always predictive of the human response.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

IX. NURSING MOTHERS

No studies in lactating animals have been conducted with the combined components of JANUMET. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin is excreted in human milk. Therefore, JANUMET should not be used by a woman who is nursing.

X. PEDIATRIC USE

The safety and efficacy of the addition of sitagliptin in pediatric patients aged 10 to 17 years with type 2 diabetes and inadequate glycemic control on metformin with or without insulin was assessed in two studies over 54 weeks. The addition of sitagliptin (administered as JANUMET or JANUMET XR) was compared to the addition of placebo to metformin or metformin XR.

While superiority of HbA_{1c} reduction was demonstrated for JANUMET/JANUMET XR over metformin at Week 20 in the pooled analysis of these two studies, results from the individual studies were inconsistent. Furthermore, efficacy for JANUMET/JANUMET XR over metformin was not observed at Week 54. Therefore, these results do not support use of JANUMET or JANUMET XR in pediatric subjects (10 to 17 years old) with type 2 diabetes.

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

JANUMET and JANUMET XR have not been studied in pediatric patients under 10 years of age.

XI. USE IN THE ELDERLY

JANUMET

Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUMET should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function (See **PRECAUTIONS**, Monitoring of Renal Function).

Sitagliptin phosphate

In clinical studies, the safety and effectiveness of sitagliptin in the elderly (≥ 65 years) were comparable to those seen in younger patients (<65 years).

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients.

XII. DRUG INTERACTIONS

Sitagliptin and metformin

Coadministration of multiple doses of sitagliptin (50 mg b.i.d.) and metformin (1000 mg b.i.d.) did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

Pharmacokinetic drug interaction studies with JANUMET have not been performed; however, such studies have been conducted with the individual components of JANUMET, sitagliptin and metformin.

Sitagliptin phosphate

In drug interaction studies, sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: metformin, rosiglitazone, glyburide, simvastatin, warfarin, and oral contraceptives. Based on these data, sitagliptin does not inhibit CYP isozymes CYP3A4, 2C8, or 2C9. Based on *in vitro* data, sitagliptin is also not expected to inhibit CYP2D6, 1A2, 2C19 or 2B6 or to induce CYP3A4.

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on sitagliptin pharmacokinetics. Medications assessed were those that are commonly administered to patients with type 2 diabetes including cholesterol-lowering agents (e.g., statins, fibrates, ezetimibe), anti-platelet agents (e.g., clopidogrel), antihypertensives (e.g., ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (e.g., naproxen, diclofenac, celecoxib), anti-depressants (e.g., bupropion, fluoxetine, sertraline), antihistamines (e.g., cetirizine), proton-pump inhibitors (e.g., omeprazole, lansoprazole), and medications for erectile dysfunction (e.g., sildenafil).

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration ($C_{\max}$, 18%) of digoxin with the coadministration of sitagliptin. These increases are not considered to be clinically meaningful. Patients receiving digoxin should be monitored appropriately. The AUC and $C_{\max}$ of sitagliptin were increased approximately 29% and 68%, respectively, in subjects with coadministration of a single 100-mg oral dose of JANUVIA™ and a single 600-mg oral dose of cyclosporine, a potent probe inhibitor of p-glycoprotein. The observed changes in sitagliptin pharmacokinetics are not considered to be clinically meaningful.

Metformin hydrochloride

Glyburide: In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Drugs that reduce metformin clearance: Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JANUMET the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

XIII. SIDE EFFECTS

In placebo-controlled clinical trials, in patients with type 2 diabetes mellitus, the combination of sitagliptin and metformin was generally well tolerated. The overall incidence of side effects reported in patients receiving the combination of sitagliptin and metformin was similar to that reported in patients receiving the combination of placebo and metformin.

Combination Therapy with Sitagliptin and Metformin

Initial Therapy

In a 24-week placebo-controlled factorial study of initial therapy with sitagliptin 50 mg twice daily in combination with metformin at 500 or 1000 mg twice daily, the drug-related adverse reactions reported in $\geq 1\%$ of patients receiving combination therapy (and greater than in patients receiving placebo) are shown in Table 1.

Table 1 Initial Therapy with Combination of Sitagliptin and Metformin: Drug-Related Adverse Reactions Reported in $\geq$ 1% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)[†]				
	Number of Patients (%)			
	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 or 1000 mg b.i.d. ^{† †}	Sitagliptin 50 mg b.i.d. + Metformin 500 or 1000 mg b.i.d. ^{† †}
	N = 176	N = 179	N = 364	N = 372
Diarrhea	2 (1.1)	0 (0.0)	12 (3.3)	13 (3.5)
Nausea	1 (0.6)	0 (0.0)	9 (2.5)	6 (1.6)
Dyspepsia	0 (0.0)	0 (0.0)	4 (1.1)	5 (1.3)
Flatulence	0 (0.0)	0 (0.0)	2 (0.5)	5 (1.3)
Vomiting	0 (0.0)	0 (0.0)	1 (0.3)	4 (1.1)
Headache	0 (0.0)	1 (0.6)	4 (1.1)	5 (1.3)
Hypoglycemia	0 (0.0)	1 (0.6)	2 (0.5)	4 (1.1)

[†] Intent-to-treat population

^{† †} Data pooled for the patients given the lower and higher doses of metformin.

Add-on Combination Therapy to Metformin

In a 24-week placebo-controlled study of sitagliptin added to ongoing metformin therapy, 464 patients on metformin were treated with sitagliptin 100 mg once daily and 237 patients were given placebo with metformin. The only drug-related adverse reaction reported that occurred with an incidence of $\geq$ 1% and higher than placebo in patients

receiving sitagliptin and metformin was nausea (100 mg sitagliptin and metformin; 1.1%, placebo and metformin, 0.4%).

Hypoglycemia and Gastrointestinal Adverse Experiences

In the placebo-controlled studies of combination therapy with sitagliptin and metformin, the incidence of hypoglycemia (regardless of investigator assessment of causality) reported in patients treated with the combination of sitagliptin and metformin was similar to that reported for patients treated with metformin and placebo. The incidences of pre-specified gastrointestinal adverse experiences in patients treated with the combination of sitagliptin and metformin were similar to those reported for patients treated with metformin alone. See Table 2.

Table 2 Hypoglycemia and Pre-specified Gastrointestinal Intestinal Adverse Experiences (Regardless of Investigator Assessment of Causality) Reported in Patients Receiving Combination Therapy†						
	Number of Patients (%)					
	Study of Sitagliptin and Metformin as Initial Therapy				Study of Sitagliptin as Add-on to Metformin	
	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 or 1000 mg b.i.d.† †	Sitagliptin 50 mg b.i.d. + Metformin 500 or 1000 mg b.i.d.† †	Placebo and Metformin ≥ 1500 mg daily	Sitagliptin 100 mg q.d. and Metformin ≥ 1500 mg daily
	N = 176	N = 179	N = 364	N = 372	N= 237	N= 464

Hypoglycemia	1 (0.6)	1 (0.6)	3 (0.8)	6 (1.6)	5 (2.1)	6 (1.3)
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)	6 (2.5)	11 (2.4)
Nausea	2 (1.1)	2 (1.1)	20 (5.5)	18 (4.8)	2 (0.8)	6 (1.3)
Vomiting	1 (0.6)	0 (0.0)	2 (0.5)	8 (2.1)	2 (0.8)	5 (1.1)
Abdominal Pain†	4 (2.3)	6 (3.4)	14 (3.8)	11(3.0)	9 (3.8)	10 (2.2)

† In the study of initial therapy, Abdominal Discomfort was included with Abdominal Pain

† † Data pooled for the patients given the lower and higher doses of metformin.

In all studies, adverse experiences of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required.

Sitagliptin in Combination with Metformin and a Sulfonylurea

In a 24-week placebo-controlled study of sitagliptin 100 mg daily added to ongoing combination treatment with glimepiride $\geq$ 4 mg daily and metformin $\geq$ 1500 mg daily, the drug-related adverse reactions reported in $\geq$ 1% of patients treated with sitagliptin (N=116) and more commonly than in patients treated with placebo (N=113) were hypoglycemia (sitagliptin, 13.8%; placebo, 0.9%) and constipation (1.7%, 0.0%).

Sitagliptin in Combination with Metformin and a PPAR γ Agonist

In a placebo-controlled study of sitagliptin 100 mg daily added to ongoing combination treatment with metformin and rosiglitazone, the drug-related adverse reactions reported through the primary time point at Week 18 in $\geq$ 1% of patients treated with sitagliptin (N=170) and more commonly than in patients treated with placebo (N=92) were: headache (sitagliptin, 2.4%; placebo, 0.0%), diarrhea (1.8%, 1.1%), nausea (1.2%, 1.1%), hypoglycemia (1.2%, 0.0%), and vomiting (1.2%, 0.0%). Through Week 54, the drug-related adverse reactions reported in $\geq$ 1% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: headache (2.4%, 0.0%),

hypoglycemia (2.4%, 0.0%), upper respiratory tract infection (1.8%, 0.0%), nausea (1.2%, 1.1%), cough (1.2%, 0.0%), fungal skin infection (1.2%, 0.0%), peripheral edema (1.2%, 0.0%), and vomiting (1.2%, 0.0%).

Sitagliptin in Combination with Metformin and Insulin

In a 24-week placebo-controlled study of sitagliptin 100 mg added to ongoing combination treatment with metformin $\geq$ 1500 mg daily and stable-dose insulin, the only drug-related adverse reaction reported in $\geq$ 1% of patients treated with sitagliptin (N=229) and more commonly than in patients treated with placebo (N=233) was hypoglycemia (sitagliptin, 10.9%; placebo, 5.2%). In another 24-week study of patients receiving sitagliptin as add-on therapy while undergoing insulin intensification (with or without metformin), the only drug-related adverse reaction reported in $\geq$ 1% in patients treated with sitagliptin and metformin and more commonly than in patients treated with placebo and metformin was vomiting (sitagliptin and metformin, 1.1%; placebo and metformin, 0.4%).

Pancreatitis

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 events 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 also TECOS Cardiovascular Safety Study, below. (See **PRECAUTIONS**, *Pancreatitis*)

With the combination of sitagliptin and metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed.

Adverse Reactions Reported with Sitagliptin

The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in $\geq 5\%$ of patients and more commonly than in patients given placebo was nasopharyngitis.

*Adverse Reactions Reported with Metformin**

The following adverse reactions may occur under treatment with metformin.

Frequencies are defined as follows: very common $\geq 1/10$; common $\geq 1/100 - <1/10$; uncommon $\geq 1/1,000 - <1/100$; rare $\geq 1/10,000 - <1/1,000$; very rare $<1/10,000$. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders:

Common:

Vitamin B₁₂ decrease/deficiency (see Precautions).

Very rare:

Lactic acidosis (see Precautions)

Nervous system disorders:

Common:

Taste disturbance

Gastrointestinal disorders:

Very common:

Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended

that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders:

Very rare:

Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:

Very rare:

Skin reactions such as erythema, pruritus, urticaria

TECOS Cardiovascular Safety Study

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 eGFR was ≥ 30 and < 50 mL/min/1.73 m²), 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.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia 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 hypoglycaemia 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.

Pediatric population

In a pooled analysis of two placebo-controlled clinical studies with JANUMET and JANUMET XR in pediatric patients aged 10 to 17 years with type 2 diabetes, the drug-related adverse reactions reported through the 54-week treatment period in $\geq 1\%$ of patients in the JANUMET/JANUMET XR group (N=107) and more commonly than in patients in the Metformin/Metformin XR group (N=113) were diarrhea (JANUMET/JANUMET XR, 2.8%; Metformin/Metformin XR, 0.9%), nausea (2.8%, 0.9%), and hypoglycemia (6.5%, 3.5%).

The profile of side effects was comparable to that observed in adults. There were no clinically relevant differences between the JANUMET/JANUMET XR and Metformin/Metformin XR groups through Week 54 in laboratory safety endpoints, vital signs, indices of adiposity, or growth and development endpoints.

Postmarketing Experience:

Additional adverse reactions have been identified during postmarketing use of JANUMET or sitagliptin, one of the components of JANUMET. These reactions have been reported when JANUMET or sitagliptin have been used alone 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 **CONTRAINDICATIONS** and **PRECAUTIONS**, *Sitagliptin phosphate, Hypersensitivity Reactions*); acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see **PRECAUTIONS**, *Pancreatitis*); worsening renal function, including acute renal failure (sometimes requiring dialysis); bullous pemphigoid (see **PRECAUTIONS**, *Bullous Pemphigoid*); severe and disabling arthralgia

(see **PRECAUTIONS**, *Severe and Disabling Arthralgia*); upper respiratory tract infection; nasopharyngitis; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; thrombocytopenia.

XIIIa. Laboratory Test Findings

Sitagliptin phosphate

The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin and metformin compared to patients treated with placebo and metformin. Across clinical studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to a small increase in neutrophils. This observation was seen in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant.

Metformin hydrochloride

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B₁₂ supplementation (see **PRECAUTIONS**, *Metformin hydrochloride*).

XIV. OVERDOSAGE

Sitagliptin phosphate

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin (see **CLINICAL PHARMACOLOGY**, *Pharmacodynamics, Cardiac Electrophysiology*). 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 periods of 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 if required.

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.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **PRECAUTIONS**, *Metformin hydrochloride*). 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.

XV. APPEARANCE & AVAILABILITY

JANUMET 50/500 mg Tablet: Light pink, film-coated tablet, debossed '575' on one side and blank on the other. It is available in trade packs of 28s and 56s. It is also available in sample packs of 14s and 28s.

JANUMET 50/850 mg Tablet: Pink, film-coated tablet, debossed '515' on one side and blank on the other. It is available in trade packs of 28s and 56s.

JANUMET 50/1000 mg Tablet: Red, film-coated tablet, debossed '577' on one side and blank on the other. It is available in trade packs of 28s and 56s.

XVI. STORAGE

Store below 30°C (86°F).

XVII. SHELF-LIFE

Please refer to expiry on the outer carton.

XVIII. MANUFACTURED BY

MSD International GmbH (Singapore Branch)
70 Tuas West Drive, Pharma West Tablet facility,
Singapore, SG-638414, Singapore

XIX. PACKED BY

Merck Sharp & Dohme B.V.
Waarderweg 39,

2031 BN, Haarlem,
Netherlands.

XX. PRODUCT REGISTRATION HOLDER
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MERCK SHARP & DOHME (MALAYSIA) SDN. BHD.

Lot No. B-22-1 & B-22-2, Level 22

The Ascent, Paradigm No. 1

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