Tablet

JANUVIA®

(sitagliptin phosphate)

I. THERAPEUTIC CLASS

JANUVIA* (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 insulinotropic 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 (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

II. COMPOSITION

IIa. Active Ingredients

Each film-coated tablet of JANUVIA contains 32.13, 64.25 or 128.5 mg of sitagliptin phosphate monohydrate, which is equivalent to 25, 50 or 100 mg, respectively, of free base.

III. CLINICAL PHARMACOLOGY

IIIa. Mechanism of Action

JANUVIA is a member of a class of oral anti-hyperglycemic 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 insulinotropic 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 such that 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 release is enhanced as glucose rises above normal concentrations. Further, 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. 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 post-prandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulfonylureas, which increase insulin secretion even when glucose levels are low and can lead to 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.

IIIb. Pharmacokinetics

The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM• hr, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100-mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

IIIb-1. Absorption

The absolute bioavailability of sitagliptin is approximately 87%. Since co-administration of a high-fat meal with JANUVIA had no effect on the pharmacokinetics, JANUVIA may be administered with or without food.

IIIb-2. Distribution

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

IIIb-3. Metabolism

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 [^{14}C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

IIIb-4. Elimination

Following administration of an oral [^{14}C] sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

IIIb-5. Characteristics in Patients

Renal Impairment: A single-dose, open-label study was conducted to evaluate the pharmacokinetics of JANUVIA (50-mg dose) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with ESRD on hemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses.

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

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

patients with eGFR <45 mL/min/1.73 m^2. (see **DOSAGE AND ADMINISTRATION**, *Patients with Renal Impairment*.)

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

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

Elderly: No dosage adjustment is required based on age. 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.

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.

Gender: No dosage adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Race: No dosage adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of 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.

Body Mass Index (BMI): No dosage adjustment is necessary based on BMI. Body mass index had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

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

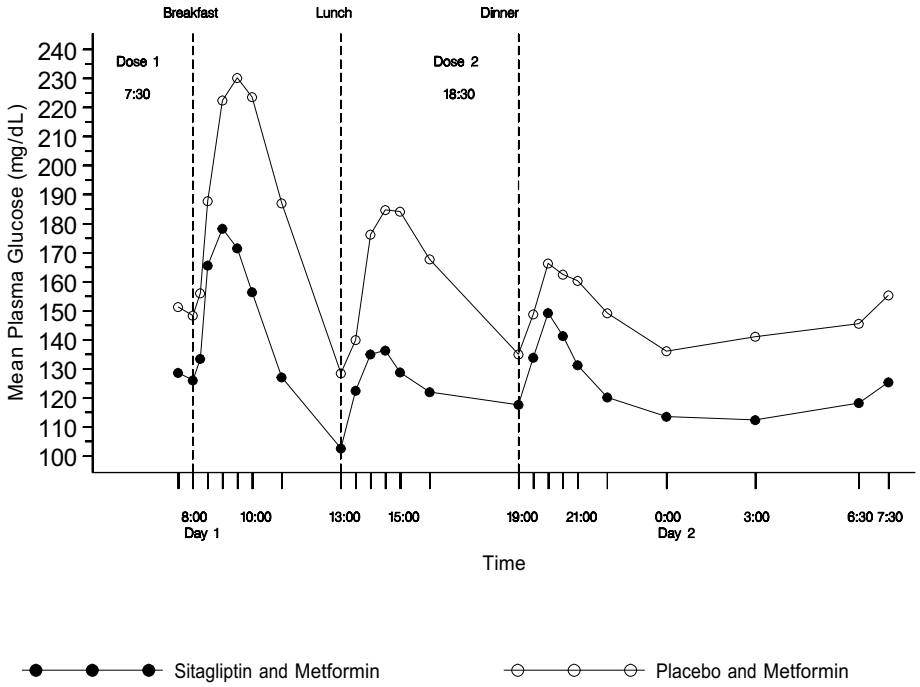
IIIc. Pharmacodynamics

General

In patients with type 2 diabetes, administration of single oral doses of JANUVIA 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 a study of patients with type 2 diabetes inadequately controlled on metformin monotherapy, glucose levels monitored throughout the day were significantly lower in patients who received sitagliptin 100 mg per day (50 mg twice daily) in combination with metformin compared with patients who received placebo with metformin (see Figure 1).

Figure 1: 24-hour Plasma Glucose Profile after 4-Week Treatment with Sitagliptin 50 mg BID with Metformin or Placebo with Metformin



In Phase III clinical studies of 18- and 24-week duration, treatment with JANUVIA 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, JANUVIA 50 mg twice daily provided no additional glycemic efficacy compared to 100 mg once daily.

In a randomized, placebo-controlled, double-blind, double-dummy, four-period crossover study in healthy adult subjects, the effects on post-meal plasma concentrations of active and total GLP-1 and glucose after co-administration 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 by approximately 2-fold after either administration of sitagliptin alone or metformin alone compared with placebo. The effect on active GLP-1 concentrations after co-administration 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, JANUVIA 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), co-administration with JANUVIA was generally well tolerated. In these patients, JANUVIA had a modest blood pressure lowering effect; 100 mg per day of JANUVIA 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 JANUVIA 100 mg, JANUVIA 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 JANUVIA 100 mg (N=81) or JANUVIA 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.

IIId. Clinical Studies

There were approximately 5200 patients with type 2 diabetes randomized in nine double-blind, placebo-controlled Phase III clinical studies conducted to evaluate the effects of sitagliptin on glycemic control. Co-morbid diseases, including dyslipidemia and hypertension, were common in the patients studied and more than 50% were obese (BMI ≥ 30 kg/m^2). The majority of patients met National Cholesterol Education Program (NCEP) criteria for metabolic syndrome. These studies included white, Hispanic, black, Asian, and other racial and ethnic groups, and patients had an overall mean age of approximately 55 years.

Additional double-blind, placebo-controlled clinical studies were conducted, one in 151 Japanese patients with type 2 diabetes and another in 91 patients with type 2 diabetes and moderate to severe renal insufficiency.

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

In patients with type 2 diabetes, treatment with JANUVIA produced clinically significant improvements in hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG) and 2-hour post-prandial glucose (PPG) compared to placebo. In the active (glipizide)-controlled study, clinically significant improvements in glycemic control were maintained for 52 weeks. JANUVIA provided improvement in measures of beta cell function (see **CLINICAL PHARMACOLOGY, *Pharmacodynamics***).

Clinical Studies Monotherapy

A total of 1262 patients with type 2 diabetes participated in two double-blind, placebo-controlled studies, one of 18-week and another of 24-week duration, to evaluate the efficacy and safety of JANUVIA monotherapy. Patients with inadequate glycemic control (HbA_{1c} 7% to 10%) were randomized to receive a 100-mg or 200-mg dose of JANUVIA or placebo once daily.

Treatment with JANUVIA at 100 mg daily provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo (Tables 1 and 2). These studies included patients with a wide range of baseline HbA_{1c}. The improvement in HbA_{1c} compared to placebo was not affected by gender, age, race, prior antihyperglycemic therapy, baseline BMI, presence of metabolic syndrome, or a standard index of insulin resistance (HOMA-IR). Patients with a shorter length of time since diagnosis of diabetes (<3 years) or with higher baseline HbA_{1c} had greater reductions

in HbA_{1c}. In the 18- and 24-week studies, among patients who were not on an antihyperglycemic agent at study entry, the reduction from baseline in HbA_{1c} was -0.67% and -0.85%, respectively, for those given JANUVIA and -0.10% and -0.18%, respectively, for those given placebo. In both studies, JANUVIA provided a significant reduction compared with placebo in FPG (-19.3 mg/dL in the 18-week study and -15.8 mg/dL in the 24-week study) at 3 weeks, the first time point at which FPG was measured. Overall, the 200-mg daily dose did not provide greater glycemic efficacy than the 100-mg daily dose. The effect of JANUVIA on lipid endpoints was similar to placebo. Body weight did not increase from baseline with JANUVIA therapy in either study, compared to a small reduction in patients given placebo (Table 2). The observed incidence of hypoglycemia in patients treated with JANUVIA was similar to placebo.

Table 1

HbA_{1c} Results in 18- and 24-Week Placebo-Controlled Studies of JANUVIA in Patients with Type 2 Diabetes† , including Stratification by Baseline HbA_{1c} Category

	18-Week Study		24-Week Study	
	JANUVIA 100 mg	Placebo	JANUVIA 100 mg	Placebo
HbA_{1c} (%)	N = 193	N = 103	N = 229	N = 244
Baseline (mean)	8.04	8.05	8.01	8.03
Change from Baseline (adjusted mean‡)	-0.48	0.12	-0.61	0.18
Difference from Placebo (adjusted mean‡)	-0.60§		-0.79§	
Patients (%) achieving HbA_{1c} <7%	69 (35.8)	16 (15.5)	93 (40.6)	41 (16.8)
Baseline HbA_{1c} Category				
HbA_{1c} (%) ≥ 9% at Baseline	N = 27	N = 20	N = 37	N = 35
Baseline (mean)	9.48	9.48	9.59	9.46
Change from Baseline (adjusted mean‡)	-0.83	0.37	-1.27	0.25
Difference from Placebo (adjusted mean‡)	-1.20		-1.52	
HbA_{1c} (%) ≥ 8% to <9% at Baseline	N = 70	N = 25	N = 62	N = 82
Baseline (mean)	8.40	8.38	8.36	8.41
Change from Baseline (adjusted mean‡)	-0.42	0.19	-0.64	0.16

Difference from Placebo (adjusted mean‡)	-0.61		-0.80	
HbA_{1c} (%) <8% at Baseline	N = 96	N = 58	N = 130	N = 127
Baseline (mean)	7.37	7.41	7.39	7.39
Change from Baseline (adjusted mean‡)	-0.42	0.02	-0.40	0.17
Difference from Placebo (adjusted mean‡)	-0.44		-0.57	

† 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.

Table 2

Additional Glycemic Parameters and Body Weight in 18- and 24-Week Placebo-Controlled Studies of JANUVIA in Patients with Type 2 Diabetes†

	18-Week Study		24-Week Study	
	JANUVIA 100 mg	Placebo	JANUVIA 100 mg	Placebo
FPG (mg/dL)	N = 201	N = 107	N = 234	N = 247
Baseline (mean)	179.8	183.6	170.2	176.1
Change from baseline (adjusted mean‡)	-12.7	7.0	-12.4	4.7
Difference from Placebo (adjusted mean‡)	-19.7§		-17.1§	
2-hour PPG (mg/dL)	‖	‖	N = 201	N = 204
Baseline (mean)			257.2	270.8
Change from baseline (adjusted mean‡)			-48.9	-2.2

Difference from Placebo (adjusted mean‡)			-46.7§	
Body Weight (kg)¶	N = 172	N = 77	N = 193	N = 174
Baseline (mean)	89.5	91.3	83.9	83.3
Change from baseline (adjusted mean‡)	-0.6	-0.7	-0.2	-1.1
Difference from Placebo (adjusted mean‡)	0.1#		0.9† †	

† 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.

ǁ Data not available.

¶ All Patients as Treated (APaT) population, excluding patients given glycemic rescue therapy.

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

† † p<0.01 compared to placebo.

Additional Monotherapy Studies

A double-blind, placebo-controlled study in Japanese patients with type 2 diabetes was performed to examine the efficacy of treatment with JANUVIA 100 mg once daily compared to placebo. This study included 151 patients (75 treated with JANUVIA, 76 treated with placebo) with mean age of 55.3 years, baseline BMI of 25.2 kg/m^2, mean baseline HbA_{1C} of 7.6%, and mean baseline FPG of 163 mg/dL. After 12 weeks, JANUVIA provided a 1.05% decrease in HbA_{1C} relative to placebo (JANUVIA -0.65% change from baseline, placebo 0.41%, p<0.001). FPG decreased by 31.9 mg/dL relative to placebo (JANUVIA -22.5 mg/dL change from baseline, placebo 9.4 mg/dL, p<0.001).

A multinational, randomized, double-blind, placebo-controlled study was also conducted to assess the safety and tolerability of JANUVIA in 91 patients with type 2 diabetes and chronic renal insufficiency (creatinine clearance <50 mL/min). Patients with moderate renal insufficiency received 50 mg daily of JANUVIA and those with severe renal insufficiency or with ESRD on hemodialysis or peritoneal dialysis received 25 mg daily. In this study, the safety and tolerability of JANUVIA were generally similar to placebo. In addition, the reductions in HbA_{1C} and FPG with

JANUVIA compared to placebo were generally similar to those observed in other monotherapy studies. (See **CLINICAL PHARMACOLOGY**, ***Pharmacokinetics***, ***Characteristics in Patients,*** **Renal Impairment**.)

Initial Combination Therapy with Metformin

A total of 1091 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind, placebo-controlled factorial study designed to assess the 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 (JANUVIA) 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). An improvement in FPG, with near maximal FPG reduction, was achieved by the 3-week time point (the first 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 co-administration 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: JANUVIA 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%.

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 (JANUVIA) 100 mg QD	Metformin 500 mg bid	Sitagliptin 50 mg bid + Metformin 500 mg bid	Metformin 1000 mg bid	Sitagliptin 50 mg bid + Metformin 1000 mg bid
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 HbA1c <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 patients given 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.

Add-on Combination Therapy with Metformin

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with metformin. All patients were started on metformin monotherapy and the dose increased to at least 1500 mg per day. Patients were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily.

In combination with metformin, JANUVIA provided significant improvements in HbA_{1C}, FPG, and 2-hour PPG compared to placebo with metformin (Table 4). The improvement in HbA_{1C} compared to placebo was not affected by baseline HbA_{1C}, 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 JANUVIA demonstrated slight decreases in total cholesterol, non-HDL cholesterol and triglycerides. A similar decrease in body weight was observed for both treatment groups.

Table 4

Glycemic Parameters and Body Weight at Final Visit (24-Week Study)

for JANUVIA as Add-on Combination Therapy with Metformin†

	JANUVIA 100 mg +	Placebo +
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 HbA1c <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 patients given glycemic rescue therapy.

¶ Not statistically significant ($p \geq 0.05$) compared to placebo + metformin.

Active-Controlled Study with Glipizide

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 JANUVIA 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 JANUVIA 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 JANUVIA and 7.5 mg/dL for glipizide. In a post-hoc analysis, patients with higher baseline HbA_{1c} (≥ 9%) in both groups had greater reductions from baseline in HbA_{1c} (JANUVIA, -1.68%; glipizide, -1.76%). In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with JANUVIA and deteriorated with glipizide treatment. The incidence of hypoglycemia in the JANUVIA group (4.9%) was significantly lower than that in the glipizide group (32.0%). Patients treated with JANUVIA exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs. +1.1 kg).

Add-on Combination Therapy with Pioglitazone

A total of 353 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with pioglitazone. All patients were started on pioglitazone monotherapy at a dose of 30-45 mg per day. Patients were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Glycemic endpoints measured included HbA_{1c} and fasting glucose.

In combination with pioglitazone, JANUVIA provided significant improvements in HbA_{1c} and FPG compared to placebo with pioglitazone (Table 5). The improvement in HbA_{1c} compared to placebo was not affected by baseline HbA_{1c}, prior antihyperglycemic therapy, 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). Compared to patients taking placebo, patients taking JANUVIA demonstrated a slight decrease in triglycerides. There was no significant difference between JANUVIA and placebo in body weight change.

Table 5

Glycemic Parameters and Body Weight at Final Visit (24-Week Study)

for JANUVIA as Add-on Combination Therapy with Pioglitazone†

	JANUVIA 100 mg + Pioglitazone	Placebo + Pioglitazone
HbA_{1c} (%)	**N = 163**	**N = 174**
Baseline (mean)	8.05	8.00
Change from baseline (adjusted mean‡)	-0.85	-0.15
Difference from placebo + pioglitazone (adjusted mean‡)	-0.70§	
Patients (%) achieving HbA1c <7%	74 (45.4)	40 (23.0)
FPG (mg/dL)	**N = 163**	**N = 174**
Baseline (mean)	168.3	165.6
Change from baseline (adjusted mean‡)	-16.7	1.0
Difference from placebo + pioglitazone (adjusted mean‡)	-17.7§	
Body Weight (kg) ‖	**N = 133**	**N = 136**
Baseline (mean)	90.0	85.6
Change from baseline (adjusted mean‡)	1.8	1.5
Difference from placebo + pioglitazone (adjusted mean‡)	0.2¶	

† 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 + pioglitazone.

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

¶ Not statistically significant ($p\geq 0.05$) compared to placebo + pioglitazone.

Add-on Combination Therapy with Glimepiride or Glimepiride plus Metformin

A total of 441 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with glimepiride (≥ 4 mg per day) or glimepiride with metformin (≥ 1500 mg per day). Patients were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Glycemic endpoints measured included HbA_{1c} and fasting glucose.

In combination with glimepiride or glimepiride plus metformin, JANUVIA provided significant improvements in HbA_{1c} and FPG compared to placebo (Table 6). In the entire study population (both patients on glimepiride and patients on glimepiride with metformin), a reduction from baseline relative to placebo in HbA_{1c} of -0.74% and in FPG of -20.1 mg/dL was seen. 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). Patients treated with JANUVIA had a modest increase in body weight compared to those given placebo.

Table 6

Glycemic Parameters and Body Weight at Final Visit (24-Week Study)

for JANUVIA as Add-on Combination Therapy with Glimepiride or Glimepiride plus Metformin†

	JANUVIA 100 mg + Glimepiride	Placebo + Glimepiride	JANUVIA 100 mg + Glimepiride + Metformin	Placebo + Glimepiride + Metformin
HbA_{1c} (%)	**N = 102**	**N = 103**	**N = 115**	**N = 105**
Baseline (mean)	8.41	8.46	8.27	8.28
Change from baseline (adjusted mean‡)	-0.30	0.27	-0.59	0.30
Difference from placebo (adjusted mean‡)	-0.57§		-0.89§	
Patients (%) achieving HbA1c <7%	11 (10.8)	9 (8.7)	26 (22.6)	1 (1.0)
FPG (mg/dL)	**N = 104**	**N = 104**	**N = 115**	**N = 109**
Baseline (mean)	183.5	184.6	179.3	178.9
Change from baseline (adjusted mean‡)	-0.9	18.4	-7.8	12.9
Difference from placebo (adjusted mean‡)	-19.3¶		-20.7§	
Body Weight (kg) ‖	**N = 76**	**N = 73**	**N = 102**	**N = 74**
Baseline (mean)	85.7	81.5	86.5	84.6
Change from baseline (adjusted mean‡)	1.1	0.0	0.4	-0.7
Difference from placebo (adjusted mean‡)	1.1#		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=0.003 compared to placebo.

p=0.016 compared to placebo.

† † p=0.007 compared to placebo.

Add-on Combination Therapy with Metformin plus 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 JANUVIA 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 JANUVIA 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, JANUVIA provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo with metformin and rosiglitazone (Table 7, Figure 2) at Week 18, with improvements sustained through the end of the study. Lipid effects were generally neutral. There was no significant difference between JANUVIA and placebo in body weight change.

Table 7

Glycemic Parameters and Body Weight at Week 18 and Week 54 (Final Visit)

for JANUVIA as Add-on Combination Therapy with Metformin and Rosiglitazone†

	Week 18		Week 54	
	JANUVIA 100 mg + Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone	JANUVIA 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 (adjusted mean‡)	-59.9	-22.0	-50.7	-16.6
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).

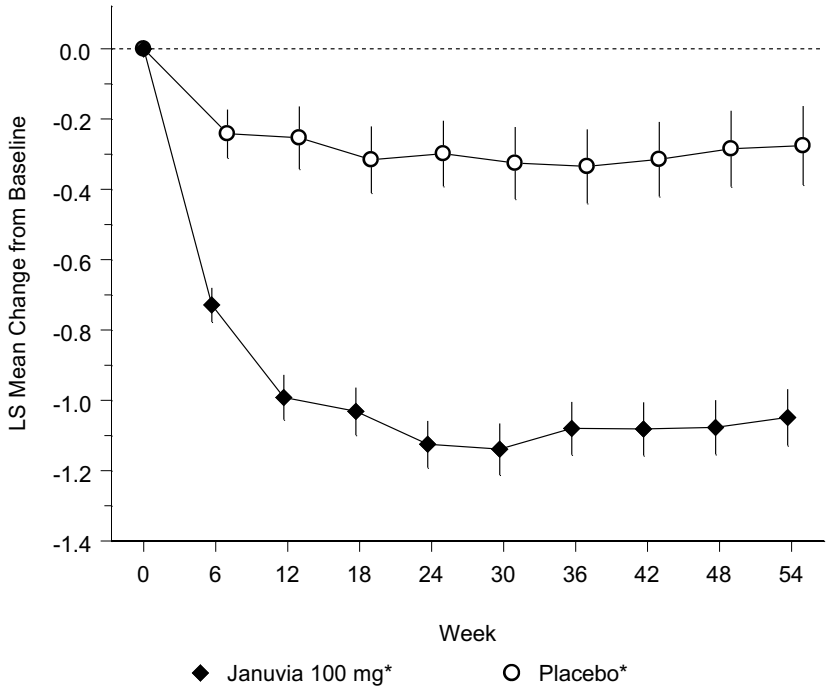
‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

§ 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.

Figure 2: Mean Change from Baseline for HbA_{1c} (%) Over 54 Weeks in a Study of JANUVIA 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.

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

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA as add-on combination therapy with a stable dose of insulin (with or without metformin). Patients on pre-mixed, long-acting, or intermediate-acting insulin with or without metformin (≥ 1500 mg per day) were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Glycemic endpoints measured included HbA_{1c}, fasting glucose, and 2-hour post-prandial glucose.

In combination with insulin (with or without metformin), JANUVIA provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo (Table 8). 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, and standard indices of insulin resistance (HOMA-IR) and insulin secretion (HOMA-β). There was no significant difference between JANUVIA and placebo in body weight change.

Table 8

Glycemic Parameters and Body Weight at Final Visit (24-Week Study)

for JANUVIA as Add-on Combination Therapy with a Stable Dose of Insulin (with or without Metformin)†

	JANUVIA 100 mg + Insulin (+/- Metformin)	Placebo + Insulin (+/- Metformin)
HbA_{1c} (%)	**N = 305**	**N = 312**
Baseline (mean)	8.72	8.64
Change from baseline (adjusted mean‡)	-0.59	-0.03
Difference from placebo (adjusted mean‡ ,§)	-0.56‖	
Patients (%) achieving HbA1c <7%	39 (12.8)	16 (5.1)
FPG (mg/dL)	**N = 310**	**N = 313**
Baseline (mean)	175.8	179.1
Change from baseline (adjusted mean‡)	-18.5	-3.5
Difference from placebo (adjusted mean‡)	-15.0‖	
2-hour PPG (mg/dL)	**N = 240**	**N = 257**
Baseline (mean)	290.9	292.1
Change from baseline (adjusted mean‡)	-30.9	5.2
Difference from placebo (adjusted mean‡)	-36.1‖	
Body Weight (kg)¶	**N = 266**	**N = 266**
Baseline (mean)	86.6	87.4
Change from baseline (adjusted mean‡)	0.1	0.1
Difference from placebo (adjusted mean‡)	0.0#	

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

‡ Least squares means adjusted for metformin use at Visit 1 (yes/no), insulin use at Visit 1 (pre-mixed vs. non-pre-mixed [intermediate- or long-acting]), and baseline value.

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

‖ p<0.001 compared to placebo.

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

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

In another 24-week, randomized, double-blind, placebo-controlled study designed to assess the insulin-sparing efficacy of JANUVIA 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 JANUVIA (N=330) or placebo (N=330), administered once daily while undergoing intensification of insulin therapy. Baseline HbA_{1c} was 8.74% and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. Glycemic endpoints measured included HbA_{1c} and FPG.

At Week 24, the increase in daily insulin dose was 20% smaller in patients treated with JANUVIA (19 IU/day) than in patients treated with placebo (24 IU/day). The difference in insulin dose (-5 IU/day) was statistically significant (p=0.009). The reduction in HbA_{1c} in patients treated with JANUVIA and insulin (with or without metformin) was -1.31% compared to -0.87% in patients treated with placebo and insulin (with or without metformin), a difference of -0.45% [95% CI: -0.60, -0.29]. The reduction in FPG in patients treated with JANUVIA and insulin (with or without metformin) was -55.5 mg/dL compared to -44.8 mg/dL in patients treated with placebo and insulin (with or without metformin), a difference of -10.7 mg/dL [95% CI: -17.2, - 4.3]. The incidence of hypoglycemia was 25.2% in patients treated with JANUVIA and insulin (with or without metformin) and 36.8% in patients treated with placebo and insulin (with or without metformin). The difference in incidence of hypoglycemia (-11.6%) was statistically significant (p=0.001).

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 JANUVIA (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and <50 mL/min/1.73 m^2) or placebo (7,339) added to usual care targeting regional standards for HbA_{1C} and CV risk factors. Patients with an eGFR <30 mL/min/1.73 m^2 were not to be enrolled in the study. The study population included 2,004 patients ≥ 75 years of age and 3,324 patients with renal impairment (eGFR <60 mL/min/1.73 m^2).

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

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

After a median follow up of 3 years, JANUVIA, 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 JANUVIA in patients with type 2 diabetes (Table 9).

Table 9

Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	JANUVIA 100 mg		Placebo			
	N (%)	Incidence Rate per 100 Patient-Years*	N (%)	Incidence Rate per 100 Patient-Years*	Hazard Ratio (95% CI)	p-value†
Analysis in the Per-Protocol Population						
Number of Patients	**7,257**		**7,266**			
Primary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina)	695 (9.6)	3.7	695 (9.6)	3.8	0.98 (0.88-1.09)	<0.001
Secondary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke)	609 (8.4)	3.2	602 (8.3)	3.3	0.99 (0.89–1.11)	<0.001
Analysis in the Intention-to-Treat Population						
Number of Patients	**7,332**		**7,339**			
Primary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2	0.98 (0.89–1.08)	<0.001
Secondary Composite Endpoint	745	3.6	746	3.6	0.99	<0.001

(Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke)	(10.2)		(10.2)		(0.89–1.10)	
Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89-1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81–1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79–1.19)	0.760
Hospitalization for unstable angina	116 (1.6)	0.5	129 (1.8)	0.6	0.90 (0.70–1.16)	0.419
Death from any cause	547 (7.5)	2.5	537 (7.3)	2.5	1.01 (0.90–1.14)	0.875
Hospitalization for heart failure‡	228 (3.1)	1.1	229 (3.1)	1.1	1.00 (0.83–1.20)	0.983

* Incidence rate per 100 patient-years is calculated as 100 × (total number of patients with ≥ 1 event during eligible exposure period per total patient-years of follow-up).

† Based on a Cox model stratified by region. For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard ratio is less than 1.3. For all other endpoints, the p-values correspond to a test of differences in hazard rates.

‡ The analysis of hospitalization for heart failure was adjusted for a history of heart failure at baseline.

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

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

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

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

IV. INDICATIONS

Monotherapy

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

Combination with metformin

JANUVIA is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin as initial therapy or when the single agent alone, with diet and exercise, does not provide adequate glycemic control. Initial combination therapy or maintenance of combination therapy may not be appropriate for all patients. These management options are left to the discretion of the health care provider.

Combination with a sulphonylurea

Januvia is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a sulphonylureas when treatment with maximal tolerated dose of sulphonylurea alone, with diet and exercise, does not provide adequate glycemic control and when metformin is inappropriate due to contraindications or intolerance.

Combination with metformin and a sulphonylurea

Januvia is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulphonylurea when dual therapy with these two agents and with diet and exercise does not provide adequate glycemic control.

Combination with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist

JANUVIA is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a PPARγ agonist (i.e. thiazolidinediones) when diet and exercise, plus the *single agent do not provide adequate glycemic control.*

Combination with metformin and a PPARγ agonist

JANUVIA is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a PPARγ agonist (i.e., thiazolidinediones) when dual therapy with these agents, with diet and exercise, does not provide adequate glycemic control.

Combination with Insulin

JANUVIA is indicated in patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control in combination with insulin (with or without metformin).

V. DOSAGE AND ADMINISTRATION

The recommended dose of JANUVIA is 100 mg once daily as monotherapy or as combination therapy with metformin, a sulfonylurea, insulin (with or without metformin), a PPARγ agonist (i.e., thiazolidinediones), metformin plus a sulfonylurea, or metformin plus a PPARγ agonist. JANUVIA can be taken with or without food.

When JANUVIA is used in combination with a sulfonylurea or with insulin, a lower dose of sulfonylurea or insulin may be considered to reduce the risk of sulfonylurea- or insulin-induced hypoglycaemia. (See **PRECAUTIONS,** *Hypoglycemia in Combination with a Sulfonylurea or with Insulin)*

Patients with Renal Impairment

Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of JANUVIA and periodically thereafter.
For patients with mild renal impairment (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2), no dosage adjustment for JANUVIA is required.

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

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

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

Pediatric population

JANUVIA should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. JANUVIA has not been studied in pediatric patients under 10 years of age.

VI. CONTRAINDICATIONS

1. JANUVIA is contraindicated in patients who are hypersensitive to any components of this product. (See **PRECAUTIONS**, *Hypersensitivity Reactions* and **SIDE EFFECTS**, *Postmarketing Experience*).

VII. PRECAUTIONS

General

JANUVIA 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, JANUVIA and other potentially suspect medicinal products should be discontinued.

Use in Patients with Renal Impairment: JANUVIA is renally excreted. To achieve plasma concentrations of JANUVIA similar to those in patients with normal renal function, lower dosages are recommended in patients with eGFR< 45 mL/min/1.73 m^2), as well as in ESRD patients

requiring hemodialysis or peritoneal dialysis. (See **DOSAGE AND ADMINISTRATION**, *Patients with Renal Impairment.*)

Hypoglycemia in Combination with a Sulfonylurea or with Insulin: In clinical trials of JANUVIA as monotherapy and JANUVIA as part of combination therapy with agents not known to cause hypoglycemia (i.e., metformin or a PPARγ agonist (thiazolidinedione)), rates of hypoglycemia reported with JANUVIA were similar to rates in patients taking placebo. As is typical with other antihyperglycemic agents, hypoglycemia has been observed when JANUVIA 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 JANUVIA. 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 JANUVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA, assess for other potential causes for the event, and institute alternative treatment for diabetes. (See **CONTRAINDICATIONS** and **SIDE EFFECTS**, *Postmarketing Experience*.)

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.

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 JANUVIA. If bullous pemphigoid is suspected, JANUVIA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

VIII. PREGNANCY

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.

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

IX. NURSING MOTHERS

Sitagliptin is secreted in the milk of lactating rats. It is not known whether sitagliptin is secreted in human milk. Therefore, JANUVIA should not be used by a woman who is nursing.

X. PEDIATRIC USE

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

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

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

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

XI. USE IN THE ELDERLY

In clinical studies, the safety and effectiveness of JANUVIA in the elderly (≥ 65 years) were comparable to those seen in younger patients (<65 years). No dosage adjustment is required based on age. Elderly patients are more likely to have renal impairment; as with other patients, dosage adjustment may be required in the presence of significant renal impairment (see DOSAGE AND ADMINISTRATION, *Patients with Renal Impairment*).

XII. DRUG INTERACTIONS

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.

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

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. 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 co-administration of sitagliptin. These increases are not considered to be clinically meaningful. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or JANUVIA is recommended.

The AUC and C_{max} of sitagliptin were increased approximately 29% and 68%, respectively, in subjects with co-administration 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. No dosage adjustment for JANUVIA is recommended when co-administered with cyclosporine or other p-glycoprotein inhibitors (e.g., ketoconazole).

XIII. SIDE EFFECTS

JANUVIA was generally well tolerated in controlled clinical studies as both monotherapy and combination therapy, with discontinuation of therapy due to clinical adverse experiences similar to placebo.

In four placebo-controlled clinical studies, as both monotherapy (one study of 18- and one of 24-week duration) and add-on combination therapy with metformin or pioglitazone (both of 24-week duration), there were 1082 patients treated with JANUVIA 100 mg once daily and 778 patients given placebo. (Two of these studies also included 456 patients treated with JANUVIA 200 mg daily, two times the recommended daily dose.) There were no drug-related adverse reactions reported that occurred with an incidence of ≥ 1% in patients receiving JANUVIA 100 mg. Overall, the safety profile of the 200-mg daily dose was similar to that of the 100-mg daily dose.

In a prespecified pooled analysis of the above studies, the overall incidence of adverse experiences of hypoglycemia in patients treated with JANUVIA 100 mg was similar to placebo (1.2% vs. 0.9%). The incidences of selected gastrointestinal adverse experiences in patients treated with JANUVIA or placebo were: abdominal pain (JANUVIA, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), vomiting (0.8%, 0.9%), and diarrhea (3.0%, 2.3%).

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

Add-on Combination with a Sulfonylurea: In a 24-week placebo-controlled study of JANUVIA 100 mg in combination with glimepiride or with glimepiride and metformin (JANUVIA, N=222; placebo, N=219), the drug-related adverse reaction reported in ≥ 1% of patients treated with

JANUVIA and more commonly than in patients treated with placebo was hypoglycemia (JANUVIA, 9.5%; placebo, 0.9%).

Add-on Combination with Metformin and a PPARγ Agonist: In a placebo-controlled study of JANUVIA 100 mg in combination with metformin and rosiglitazone (JANUVIA, N=170; placebo, N=92), the drug-related adverse reactions reported through the primary time point at Week 18 in ≥ 1% of patients treated with JANUVIA and more commonly than in patients treated with placebo were: headache (JANUVIA, 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 ≥ 1% of patients treated with JANUVIA 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%).

Initial Combination Therapy with Metformin: In a 24-week placebo-controlled factorial study of initial therapy with sitagliptin 100 mg in combination with metformin at 1000 mg or 2000 mg per day (administered as sitagliptin 50 mg/metformin 500 mg or 1000 mg twice daily), the drug-related adverse reactions reported in ≥ 1% of patients treated with sitagliptin plus metformin (N=372) and more commonly than in patients treated with metformin alone (N=364) were: diarrhea (sitagliptin plus metformin, 3.5%; metformin, 3.3%), dyspepsia (1.3%; 1.1%), flatulence (1.3%; 0.5%), vomiting (1.1%; 0.3%), and headache (1.3%; 1.1%). The incidence of hypoglycemia was 1.1% in patients given sitagliptin in combination with metformin and 0.5% in patients given metformin alone.

Initial Combination Therapy with a PPARγ Agonist: In a 24-week study of initial therapy with JANUVIA at 100 mg/day in combination with pioglitazone at 30 mg/day, the only drug-related adverse reaction reported in ≥ 1% of patients treated with JANUVIA with pioglitazone (N=261) and more commonly than in patients treated with pioglitazone alone (N=259) was (asymptomatic) decreased blood glucose (JANUVIA with pioglitazone, 1.1%; pioglitazone, 0.0%). The incidence of (symptomatic) hypoglycemia was 0.4% in patients given JANUVIA in combination with pioglitazone and 0.8% in patients given pioglitazone.

Add-on Combination with Insulin: In a 24-week placebo-controlled study of JANUVIA 100 mg in combination with stable-dose insulin (with or without metformin), the drug-related adverse

reactions reported in ≥ 1% of patients treated with JANUVIA (N=322) and more commonly than in patients treated with placebo (N=319) were: hypoglycemia (JANUVIA, 9.6%; placebo, 5.3%), influenza (1.2%, 0.3%), and headache (1.2%, 0.0%). In another 24-week study of patients receiving JANUVIA as add-on therapy while undergoing insulin intensification (with or without metformin), there were no drug-related adverse reactions reported that occurred with an incidence of ≥ 1% in patients treated with JANUVIA 100 mg and more commonly than in patients treated with placebo.

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 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*).

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

TECOS Cardiovascular Safety Study: The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with JANUVIA, 100 mg daily (or 50 mg daily if the baseline estimated glomerular filtration rate (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 study population included a total of 2,004 patients ≥ 75 years of age (970 treated with JANUVIA and 1,034 treated with placebo). The overall incidence of serious adverse events in patients receiving JANUVIA was similar to that in patients receiving placebo. Assessment of pre-specified diabetes-related complications revealed similar incidences between groups including infections (18.4% of the JANUVIA-treated patients and 17.7% of the placebo-treated patients) and renal failure (1.4% of JANUVIA-treated patients and 1.5% of placebo-treated patients). The adverse event profile in patients ≥ 75 years of age was generally similar to the overall population.
In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 2.7% in JANUVIA-treated patients and 2.5% in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 1.0% in JANUVIA-treated patients and 0.7% in placebo-treated patients. The incidence of adjudication-confirmed

pancreatitis events was 0.3% in JANUVIA-treated patients and 0.2% in placebo-treated patients. The incidence of adjudication-confirmed malignancy events was 3.7% in JANUVIA-treated patients and 4.0% in placebo-treated patients.

Pediatric population: In a clinical study with JANUVIA 100 mg in pediatric patients aged 10 to 17 years with type 2 diabetes, there were no drug-related adverse reactions reported through the 54-week treatment period in more than 1 patient in the JANUVIA group (N=95) and more commonly than in patients in the placebo group (N=90).

There were no clinically relevant differences between the JANUVIA and placebo 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 JANUVIA as monotherapy and/or in combination with other antihyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria; cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome (see **CONTRAINDICATIONS** and **PRECAUTIONS**, *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

The incidence of laboratory adverse experiences was similar in patients treated with JANUVIA 100 mg compared to patients treated with placebo. 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 an 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.

XIV. OVERDOSAGE

During controlled clinical trials in healthy subjects, single doses of up to 800 mg JANUVIA 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 JANUVIA (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 JANUVIA 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.

XV. APPEARANCE AND AVAILABILITY

JANUVIA 25mg: Pink, round, biconvex, film-coated tablet with “221” on one side and plain on the other. Available in packs of 28s.

JANUVIA 50mg: Light beige, round, biconvex, film coated tablet with “112” on one side and plain on the other. Available in packs of 28s.

JANUVIA 100mg: Beige, round, biconvex, film coated tablet with “277” on one side and plain on the other. Available in packs of 14s (sample) and 28s (trade).

XVI. STORAGE

Store below 30°C (86°F).

XVII. SHELF LIFE

Please refer to the expiry date on the outer carton.

XVIII. MANUFACTURER

Organon Pharma (UK) Limited
Shotton Lane, Cramlington,
NE23 3JU, United Kingdom

XIX. PACKER

Hangzhou Merck Sharp & Dohme Pharmaceutical Co., Ltd
No. 199, Wenhai North Road,
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XX. PRODUCT REGISTRATION HOLDER

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