PRODUCT INFORMATION

JANUVIA®

(sitagliptin phosphate monohydrate)

DESCRIPTION

JANUVIA (sitagliptin phosphate monohydrate) is an orally-active inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferators-activated receptor gamma (PPARg) agonists, alpha-glucosidase inhibitors, and amylin analogues.

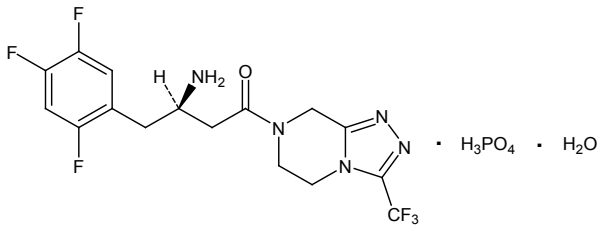
JANUVIA is available for oral use as film coated tablets containing sitagliptin phosphate monohydrate equivalent to 25, 50 or 100 mg of free base.

Each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate (calcium hydrogen phosphate, anhydrous), croscarmellose sodium, magnesium stearate and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, macrogol 3350, talc purified, titanium dioxide, iron oxide red CI77491 and iron oxide yellow CI77492.

Sitagliptin phosphate monohydrate

The chemical name of sitagliptin phosphate monohydrate is 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate. The CAS Registry Number is 654671-77-9.

The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32. The structural formula is:



Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

PHARMACOLOGY

Mechanism of Action

Sitagliptin is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycaemic 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 physiological 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 signalling 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 markedly enhanced as glucose rises above normal concentrations. GLP-1 does not impair the normal glucagon response to hypoglycaemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyses 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 hypoglycaemia in patients with type 2 diabetes and in normal subjects. In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A_{1c} (HbA_{1c}) and lower fasting and postprandial glucose concentrations. Sitagliptin inhibits DPP-4 with nanomolar potency (IC_{50} 18 nM). It does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Inhibition of DPP-8 or DPP-9 is associated with toxicity in preclinical animal models and alteration of immune function *in vitro*.

Pharmacokinetics

The pharmacokinetics of sitagliptin have been extensively characterised 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.

Absorption

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

Distribution

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

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.

Elimination
Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in faeces (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, cyclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Characteristics in Patients
Renal Insufficiency
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 insufficiency compared to normal healthy control subjects. The study included patients with renal insufficiency classified on the basis of creatinine clearance as mild (50 to <80 mL/min), moderate (30 to <50 mL/min), and severe (<30 mL/min), as well as patients with end-stage renal disease (ESRD) on haemodialysis. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times 1.2}{[\text{serum creatinine (micromol/L)}]} \quad \{\times 0.85 \text{ for female patients}\}$$

Patients with mild renal insufficiency did not have a clinically meaningful increase in the plasma concentration of sitagliptin as compared to normal healthy control subjects. An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency, and an approximately 4-fold increase was observed in patients with severe renal insufficiency and in patients with ESRD on haemodialysis, as compared to normal healthy control subjects. Sitagliptin was modestly removed by haemodialysis (13.5% over a 3- to 4-hour haemodialysis 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 moderate and severe renal insufficiency, as well as in ESRD patients requiring haemodialysis. (See **DOSAGE AND ADMINISTRATION**, *Patients with Renal Insufficiency*.)

Hepatic Insufficiency
In patients with moderate hepatic insufficiency (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 insufficiency.

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

Elderly Patients
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.

Paediatric Patients
No studies with JANUVIA have been performed in paediatric patients.

Sex
No dosage adjustment is necessary based on sex of the patient. The sex of the subject 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.

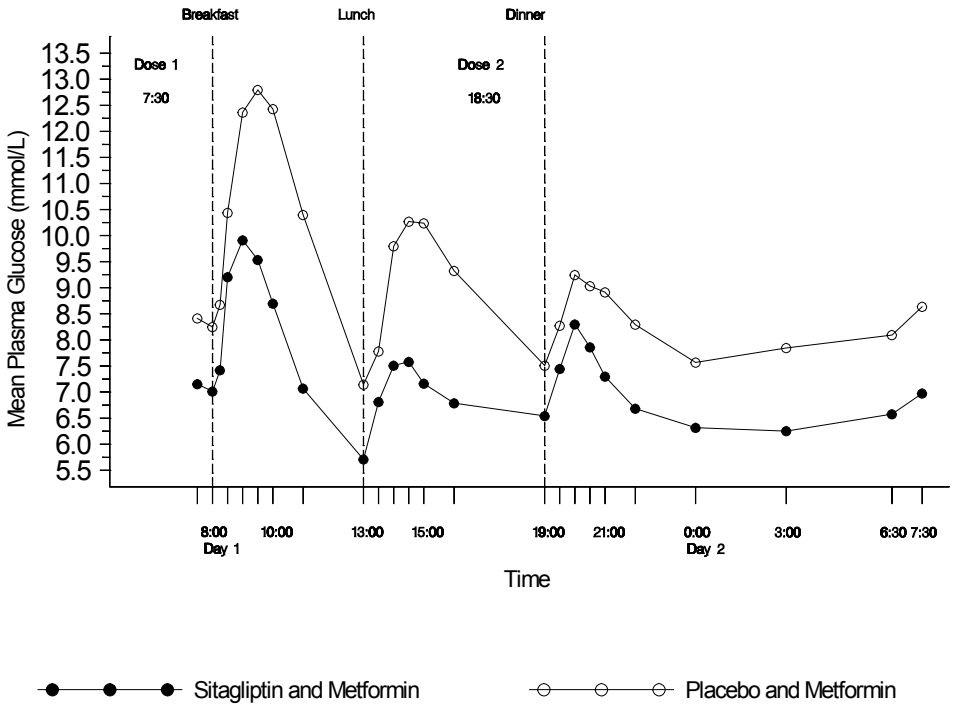
Body Mass Index
No dosage adjustment is necessary based on BMI. Body mass index had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

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

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. There are no clinical studies that demonstrate that sitagliptin alters the natural history of impaired glucose tolerance or type 2 diabetes mellitus. The durability of efficacy requires further study.

In Phase II studies, JANUVIA 50 mg twice daily provides no additional glycaemic efficacy compared to 100 mg once daily.

In studies with healthy subjects, JANUVIA did not lower blood glucose or cause hypoglycaemia, suggesting that the insulinotropic and glucagon suppressive actions of the drug are glucose dependent. (see **PRECAUTIONS**, *Hypoglycaemia in Combination with a Sulfonylurea.* See **Adverse Reactions** in respect of use with sulfonylureas.)

Effects on blood pressure

In a randomised, 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 mm Hg, as compared to placebo. Reductions have not been observed in subjects with normal blood pressure. As per good medical practice, hypertensive patients who receive JANUVIA should continue to have their blood pressure monitored.

Cardiac Electrophysiology

In a randomised, 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-fold 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.

CLINICAL STUDIES

Results from long-term studies of JANUVIA on overall morbidity and mortality outcomes are not available.

There were 2757 patients with type 2 diabetes randomised in five double-blind, placebo-controlled Phase III clinical studies conducted to evaluate the effects of sitagliptin on glycaemic control as monotherapy and in combination with metformin, pioglitazone, glimepiride, and glimepiride+metformin. Co-morbid diseases were common in the patients studied: 58% had hypertension, 54% had dyslipidaemia, and more than 50% were obese (BMI ³ 30 kg/m2). The majority of patients (51.6% to 65.8%) met National Cholesterol Education Program (NCEP) criteria for metabolic syndrome. In these studies, the mean age of patients was 55.0 years, and 62% of patients were white, 18% were Hispanic, 6% were black, 9% were Asian, and 4% were of other racial groups. The studies that support registration in general used the reduction in haemoglobin A1c (HbA1c) as the primary outcome variable. Pre-specified secondary endpoints included FPG and 2-hour PPG.

An additional double-blind, placebo-controlled clinical study was conducted 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 glycaemic control on metformin. In patients with type 2 diabetes, treatment with JANUVIA produced statistically significant improvements in haemoglobin A_{1c} (HbA_{1c}). Clinically significant improvements in HbA_{1c} were maintained for 52 weeks. Treatment with JANUVIA showed suggestions of improvement in measures of beta cell function (see **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 (443 patients) or 200-mg dose (456 patients) of JANUVIA or placebo (363 patients) once daily. JANUVIA as monotherapy is indicated for use when metformin cannot be used (see **INDICATIONS**).

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% (95% CI -0.87, -0.48) and -0.85% (95% CI -1.02, -0.68), respectively, for those given JANUVIA and -0.10% (95% CI -0.39, 0.19) and -0.18% (95% CI -0.35, -0.02), respectively, for those given placebo. In both studies, JANUVIA provided a significant reduction compared with placebo in FPG (-1.07 mmol/L in the 18-week study and -0.88 mmol/L 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. 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[‡] (95% CI))	-0.48 (-0.61, -0.35)	0.12 (-0.05, 0.30)	-0.61 (-0.74, -0.49)	0.18 (0.06, 0.30)
Difference from Placebo (adjusted mean[‡] (95% CI))	-0.60[§] (-0.82, -0.39)		-0.79[§] (-0.96, -0.62)	
Patients (%) achieving HbA_{1c} <7%	69 (35.8)	16 (15.5)	93 (40.6)	41 (16.8)
Baseline HbA_{1c} Category				
HbA_{1c} (%) ³ 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} (%) ³ 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 antihyperglycaemic therapy status and baseline value.
§ p<0.001 compared to placebo.

Table 2
Additional Glycaemic Parameters 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/dLmmol/L)	N = 201	N = 107	N = 234	N = 247
Baseline (mean)	9.98	10.19	9.46	9.78
Change from baseline (adjusted mean‡)	-0.70	0.39	-0.69	0.26
Difference from Placebo (adjusted mean‡)	-1.09§		-0.95§	
2-hour PPG (mg/dLmmol/L)	%	%	N = 201	N = 204
Baseline (mean)			14.28	15.03
Change from baseline (adjusted mean‡)			-2.71	-0.12
Difference from Placebo (adjusted mean‡)			-2.59§	

† All Patients Treated Population (an intention-to-treat analysis).
‡ Least squares means adjusted for prior antihyperglycaemic therapy status and baseline value.
§ p<0.001 compared to placebo.
% Data not available.
¶ All Patients as Treated (APaT) population, excluding patients given glycaemic rescue therapy.
# Not statistically significant (p³ 0.05) compared to placebo.
†† p<0.01 compared to placebo.

These two studies were extended to examine the efficacy and safety of sitagliptin monotherapy long-term. In the 24 week study, patients receiving placebo were redistributed (1:1) between the 2 sitagliptin doses (100 mg q.d. or 200 mg q.d.) for an 80-week single-blind (blind to dose) treatment period. Patients in the sitagliptin treatment groups in Phase A continued on the same dose of sitagliptin during the single-blind treatment period (Phase B).

In the 18 week study, patients receiving placebo were started on therapy with pioglitazone at a dose of 30 mg q.d. for a 36-week active-controlled double-blind treatment period. Patients in a sitagliptin treatment group continued on the same dose of sitagliptin during the active-controlled, double-blind treatment period. Patients in the placebo/pioglitazone arm showed a -0.87% reduction in HbA_{1c} at Week 54, compared to -0.28% and -0.19% for the sitagliptin 100 mg and 200 mg groups, respectively.

Treatment with sitagliptin 100 mg q.d. and 200 mg q.d. provided similar reductions in glycaemic parameters over the duration of each study.

Active-Controlled Study with Metformin
The efficacy of JANUVIA compared to that of metformin was evaluated in a 24-week, double-blind, metformin-controlled trial in patients with type 2 diabetes and inadequate glycemic control on diet and exercise and who were not on antihyperglycemic therapy (patients who were treated with oral antihyperglycaemic therapy at enrolment discontinued all antihyperglycaemic therapy

for at least 4 months before beginning study therapy). In this study, patients were randomized to receive either JANUVIA 100 mg daily (N=528) or metformin (N=522) for 24 weeks. Patients receiving metformin were given an initial dosage of 500 mg/day and then titrated by the investigator to a dose of 1500 to 2000 mg/day over a period of up to 5 weeks based on tolerability. The mean dose of metformin after the titration period was approximately 1900 mg/day. Glycaemic endpoints measured included HbA_{1c} and fasting glucose.

Both treatments resulted in a statistically significant improvement in glycemic control from baseline. The mean baseline HbA_{1c} was 7.2% in the per protocol population. At 24 weeks, the least squares means adjusted reduction from baseline in HbA_{1c} were -0.43% (95%CI -0.48, -0.38) for JANUVIA 100 mg daily and -0.57% (95%CI -0.62, -0.51) for metformin group, with a difference of 0.14% (95% CI 0.06, 0.21). The difference met the pre-specified criterion for confirming comparable efficacy of the two agents. In a pre-defined subgroup analysis, patients with baseline HbA_{1c} ≥8% also had similar reductions in both groups (JANUVIA, -1.13%; metformin, -1.24%).

The reduction in FPG was -0.64 mmol/L for JANUVIA and -1.08 mmol/L for metformin. Standard indices of insulin resistance (HOMA-IR) and insulin secretion (HOMA-β) showed similar improvements in both groups. Slightly smaller proportions of patients in the JANUVIA group relative to the metformin group had an HbA_{1c} value <6.5% (33.6% vs. 39.2%) and <7.0% (68.8% vs. 75.9%) at Week 24. Slight increases were also observed in the JANUVIA group relative to the metformin group for LDL-C, non-HDL-C and total-C. Both the JANUVIA and metformin treatment groups exhibited a decrease in fasting insulin, fasting proinsulin and the proinsulin to insulin ratio, with a greater reduction observed for the metformin group in fasting proinsulin, which resulted in a larger reduction in the proinsulin to insulin ratio. A smaller increase in 1,5-anhydroglucitol at Week 24 was observed in the JANUVIA group compared to the metformin group.

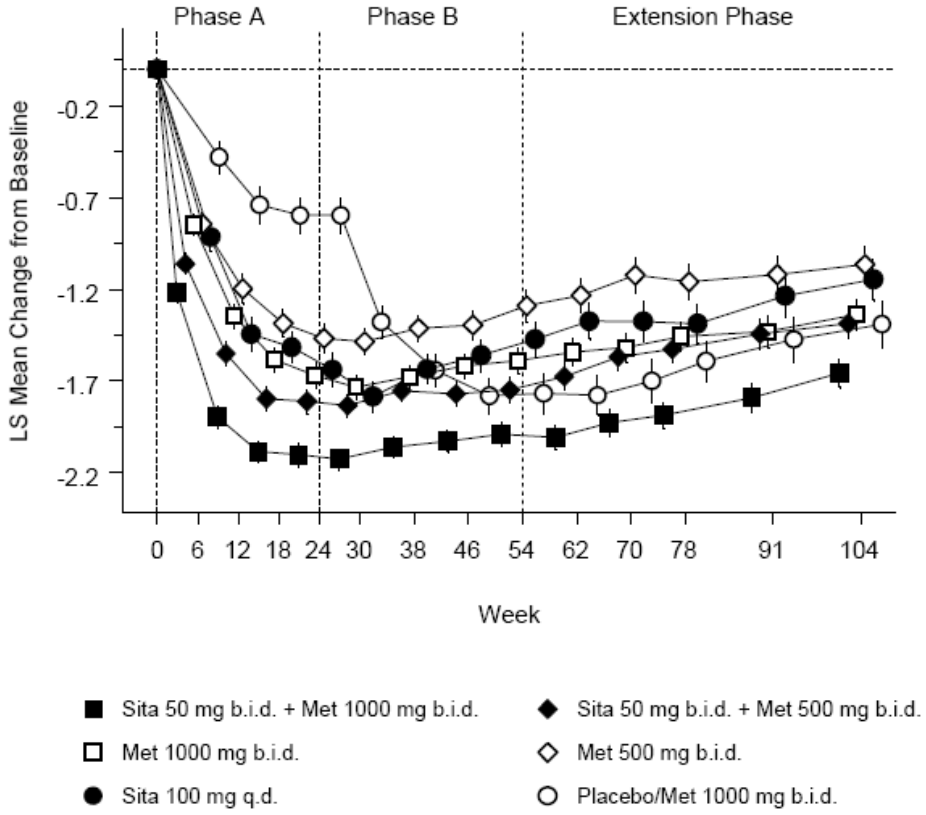
The overall incidence of gastrointestinal adverse reactions in patients treated with JANUVIA was 11.6% compared with 20.7% in patients treated with metformin. The incidence of selected gastrointestinal adverse experiences was: diarrhea (JANUVIA, 3.6%; metformin, 10.9%), nausea (1.1%, 3.1%), abdominal pain (2.1%, 3.8%), and vomiting (0.4%, 1.3%). The incidence of hypoglycemia was not significantly different between the treatment groups (JANUVIA, 1.7%; metformin, 3.4%). Body weight decreased from baseline in both treatment groups (JANUVIA, -0.6 kg; metformin -1.9 kg).

Sitagliptin and Metformin as Initial Therapy in Patients with Type 2 Diabetes
This study consisted of a 24-week, placebo-controlled Phase A, a 30-week, active-controlled Phase B, and a 50-week active-controlled Extension Phase, where 1091 patients with type 2 diabetes and inadequate glycaemic control on diet and exercise were enrolled in a, randomized, double-blind, parallel-group factorial study designed to assess the safety and efficacy of initial therapy with the combination of sitagliptin and metformin. Patients on an antihyperglycaemic agent (N=541) underwent a diet, exercise, and drug washout period of up to 12 weeks duration. After the washout period, patients with inadequate glycaemic control (A_{1C} 7.5% to 11%) were randomized after completing a 2-week single-blind placebo run-in period. Patients not on antihyperglycaemic agents at study entry (N=550) with inadequate glycaemic control (A_{1C} 7.5% to 11%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. A total of 685 patients entered the 50-week extension study, and among these patients, 517 (74.5%) completed the study. Approximately equal numbers of patients were randomized to receive initial therapy with placebo; 100 mg of sitagliptin once daily; 500 mg or

1000 mg of metformin twice daily; or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients receiving active therapy continued with their assigned treatment regimen until the end of the study, unless rescue (glibenclamide) was required. Patients receiving placebo were switched to 1000 mg of metformin twice daily at the beginning of Phase B.

Initial combination therapy with sitagliptin 100 mg and metformin 1000 mg or 2000 mg daily provides sustained improvements in HbA_{1c} and FPG and 2-hour PPG compared with either corresponding monotherapy dose over 104 weeks; (Table 3, Figure 2). 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 over time. A slight upward trend in the reduction in HbA_{1c} was observed during the extension phase in each treatment group. Measures of beta cell function, HOMA-β and the proinsulin to insulin ratio generally 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 antihyperglycaemic agent at study entry were: sitagliptin 100 mg once daily, -1.14%; metformin 500 mg bid, -1.20%; metformin 1000 mg bid, -1.22%; sitagliptin 50 mg bid with metformin 500 mg bid, -1.65%; and sitagliptin 50 mg bid with metformin 1000 mg bid, -1.74%; and for patients receiving placebo, -1.11%.

Figure 2 LS Mean Change from Baseline for HbA_{1c} over Time (LS Mean ± SE) by Treatment Group All-Patients-Treated in the Extension Phase*



* Statistical comparisons apply only to Phase A - formal statistical comparisons are not possible for Phase B and the extension phase.

Table 3
Glycaemic 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} (%)[þ]	**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 (mmol/L) [β]	**N = 169**	**N = 178**	**N = 179**	**N = 183**	**N = 179**	**N = 180**
Baseline (mean)	10.90	11.18	11.39	11.32	10.94	10.92
Change from baseline (adjusted mean[‡])	0.32	-0.97	-1.52	-2.61	-1.63	-3.55
Difference from placebo (adjusted mean[‡])	-	-1.29[§]	-1.84[§]	-2.94[§]	-1.95[§]	-3.87[§]
2-hour PPG (mmol/L) [β]	**N = 129**	**N = 136**	**N = 141**	**N = 147**	**N = 138**	**N = 152**
Baseline (mean)	15.37	15.84	16.25	16.20	15.73	15.93
Change from baseline (adjusted mean[‡])	0.02	-2.88	-2.96	-5.13	-4.33	-6.47
Difference from placebo (adjusted mean[‡])		-2.90[§]	-2.98[§]	-5.15[§]	-4.35[§]	-6.49[§]
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 antihyperglycaemic therapy status and baseline value.
§ p<0.001 compared to placebo.
% All Patients as Treated (APaT) population, excluding patients given glycaemic rescue therapy.
¶ p=0.005 compared to placebo.
# Not statistically significant (p^3 0.05) compared to placebo.
þ Primary efficacy outcome
β Secondary efficacy outcome

In addition, this study included patients (N=117) with more severe hyperglycaemia (HbA_{1c} >11% or blood glucose >15.54 mmol/L) who were treated with open-label sitagliptin at 50 mg and metformin at 1000 mg twice daily for 24 weeks, but were not eligible to enter Phase B of the study. In this group of patients, the baseline HbA_{1c} value was 11. 15%, FPG was 17.45 mmol/L, and 2-hour PPG was 24.48 mmol/L. After 24 weeks, decreases from baseline of -2.94 % for HbA_{1c}, -7.03 mmol/L for FPG, and -11.54 mmol/L 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 Therapy to Metformin

A total of 701 patients with type 2 diabetes with inadequate glycaemic control on metformin alone participated in a 24-week, randomised, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with metformin (Hb A1c 7% to 10%). All patients were started on metformin monotherapy and the dose increased to at least 1500 mg per day. Patients were randomised 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} (the primary endpoint), FPG, and 2-hour PPG compared to placebo with metformin (Table 4). A pre-specified secondary endpoint was the number of patients in each group who required therapeutic "rescue" with pioglitazone. Twenty-one of 464 patients (5%) randomised to JANUVIA and 32 of 237 patients (14%) randomised to placebo required pioglitazone "rescue".

The improvement in HbA_{1C} compared to placebo was not affected by baseline HbA_{1C}, prior anti-hyperglycaemic 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 in both treatment groups.

Table 4
Glycaemic Parameters and Body Weight at Final Visit (24-Week Study)
for JANUVIA in Combination with Metformin† - Primary (HbA_{1C}) and Secondary Outcomes

	JANUVIA 100 mg + 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 (mmol/L)	**N = 454**	**N = 226**
Baseline (mean)	9.44	9.63
Change from baseline (adjusted mean‡)	-0.94	0.47
Difference from placebo + metformin (adjusted mean‡)	-1.41§	
2-hour PPG (mmol/L)	**N = 387**	**N = 182**
Baseline (mean)	15.24	15.12
Change from baseline (adjusted mean‡)	-3.44	-0.63
Difference from placebo + metformin (adjusted mean‡)	-2.81§	
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 antihyperglycaemic therapy and baseline value.
§ p<0.001 compared to placebo + metformin.
% All Patients as Treated (APaT) population, excluding patients given glycaemic rescue therapy.
¶ Not statistically significant (p³ 0.05) compared to placebo + metformin.

Active- Controlled Study Against Glipizide as Add-on Therapy to Metformin

Long-term maintenance of effect was evaluated in a 52-week, double-blind, glipizide-controlled trial in patients with type 2 diabetes. Patients with inadequate glycaemic control on metformin at ≥1500 mg/day were randomized to treatment with 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 over the next 18 weeks, to a maximum dosage of 20 mg/day as needed to optimise glycaemic control. Thereafter, the glipizide dose was to have been kept constant. The mean dose of glipizide after the titration period was 10.3 mg. The objective of the study was to test whether sitagliptin was not inferior to glipizide, at a non-inferiority margin of 0.3%. After 52 weeks, both treatments resulted in a statistically significant improvement in glycaemic control from baseline. The reduction from baseline in HbA_{1c} (primary endpoint) was 0.67% for JANUVIA 100 mg daily and 0.67% for glipizide, confirming the noninferiority of JANUVIA compared to glipizide.

With respect to other analyses, the reduction in FPG was 0.56 mmol/L for JANUVIA and 0.42 mmol/Lfor 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%). The incidence of hypoglycaemia 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 Therapy to Pioglitazone

A total of 353 patients with type 2 diabetes inadequately controlled on pioglitazone alone participated in a 24-week, randomised, 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 randomised to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Glycaemic endpoints measured included HbA_{1c} and fasting glucose. Another pre-specified secondary endpoint was the number of patients in each group who required therapeutic “rescue” with metformin.

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 anti-hyperglycaemic 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. Twelve of 175 patients (7%) randomised to JANUVIA and 25 of 178 patients (14%) randomised to placebo required metformin “rescue”.

Table 5
Glycaemic Parameters and Body Weight at Final Visit (24-Week Study)
for JANUVIA in Combination with Pioglitazone† - Primary (HbA_{1C}) and Secondary Outcomes

	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 (mmol/L)	**N = 163**	**N = 174**
Baseline (mean)	9.34	9.19
Change from baseline (adjusted mean‡)	-0.93	0.06
Difference from placebo + pioglitazone (adjusted mean‡)	-0.98§	
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 antihyperglycaemic therapy status and baseline value.
§ p<0.001 compared to placebo + pioglitazone.
% All Patients as Treated (APaT) population, excluding patients given glycaemic rescue therapy.
¶ Not statistically significant (p³ 0.05) compared to placebo + pioglitazone.

Clinical Studies in Patients with Renal Insufficiency

A multinational, randomised, 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 haemodialysis or peritoneal dialysis received 25 mg daily. In this study, the safety and tolerability of JANUVIA were generally similar to placebo. (See **PHARMACOLOGY**, **Pharmacokinetics**, **Characteristics in Patients***, **Renal Insufficiency***).

Long Term Efficacy of Sitagliptin

Improvements in glycemic control with sitagliptin have been demonstrated over periods of up to 2 years in both the Phase II studies and Phase III studies. Importantly, the effect size and the durability of these improvements over 104-106 weeks were similar to those observed in the active-comparator groups. The observed reduction in glycaemic efficacy after initial improvement is believed to be a consequence of the natural history of the disease with continued loss of b-cell function, and/or an additional increase in insulin resistance, and/or diminishing compliance with diet and exercise, and is similar to that observed with other classes of antihyperglycaemic therapies.

INDICATIONS

JANUVIA is indicated for the treatment of diabetes mellitus type 2 in persons 18 years of age and older who have failed dietary measures and exercise:

- as monotherapy, as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus, when metformin cannot be used.
- as dual combination therapy, with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

CONTRAINDICATIONS

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

PRECAUTIONS

General

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

Pancreatitis: In postmarketing experience there have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis (see **ADVERSE REACTIONS**, *Postmarketing Experience*), in patients taking sitagliptin. Because these reports are made 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. 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 Insufficiency: Because 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 moderate and severe renal insufficiency, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis. (See **DOSAGE AND ADMINISTRATION**, *Patients with Renal Insufficiency.*)

Hypoglycaemia in Combination with a Sulfonylurea: In clinical trials of JANUVIA as monotherapy and JANUVIA as part of combination therapy with metformin or pioglitazone, rates of hypoglycaemia reported with JANUVIA were similar to rates in patients taking placebo. As typical with other antihyperglycaemic agents used in combination with sulfonylurea, when JANUVIA was used in combination with a sulfonylurea, a medication known to cause hypoglycaemia, the incidence of sulfonylurea-induced hypoglycaemia was increased over that of placebo (see **SIDE EFFECTS**). Therefore, to reduce the risk of sulfonylurea-induced hypoglycaemia, reduction in the dose of sulfonylurea may be considered (see **DOSAGE AND ADMINISTRATION**). The use of JANUVIA in combination with insulin has not been adequately studied.

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 **ADVERSE REACTIONS**, *Postmarketing Experience*.)

Effects on fertility
No adverse effects on fertility were observed in male and female rats given sitagliptin orally at doses up to 1000 mg/kg/day (approximately 100 times the AUC in humans at the clinical dose of 100 mg/day) prior to and throughout mating.

Use in Pregnancy (Category B3)
Pregnancy Category B3. Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg/day or in rabbits given up to 125 mg/kg/day during organogenesis (up to 32 and 22 times, respectively, the AUC in humans at the clinical dose of 100 mg/day). A slight increase in the incidence of foetal rib abnormalities (absent, hypoplastic and wavy ribs) was observed among foetuses of rats given sitagliptin at 1000 mg/kg/day (approximately 100 times the AUC in humans at 100 mg/day). Pups of rats administered sitagliptin at 1000 mg/kg/day from gestation day 6 to lactation day 20 showed reduced birth weight and postnatal body weight gain (observed prior to and after weaning). No functional or behavioural toxicity was observed in the offspring of treated rats.

Sitagliptin crosses the placenta in rats and rabbits.

There are no adequate and well-controlled studies with JANUVIA in pregnant women. JANUVIA, like other oral antihyperglycaemic agents, is not recommended for use in pregnancy.

Use in Lactation
Treatment of rats with sitagliptin during pregnancy and lactation caused decreased pup body weight gain (see Use in Pregnancy). Sitagliptin is excreted in the milk of lactating rats at a milk to plasma ratio of 4:1. It is not known whether sitagliptin is excreted in human milk. Therefore, JANUVIA should not be used by a woman who is nursing.

Use in the Elderly
In clinical studies, the safety and effectiveness of JANUVIA in the elderly (³ 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 insufficiency; as with other patients, dosage adjustment may be required in the presence of significant renal insufficiency (see **DOSAGE AND ADMINISTRATION**, *Patients with Renal Insufficiency*).

Use in Paediatric Patients
Safety and effectiveness of JANUVIA in paediatric patients under 18 years have not been established.

Carcinogenicity
A two-year carcinogenicity study was conducted in rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of focal eosinophilic cellular alterations

in the liver in both sexes at 150 mg/kg/day and at 500 mg/kg/day. There was an increased incidence of basophilic cellular alterations in females at 500 mg/kg/day. Eosinophilic and basophilic cellular alterations are regarded as preneoplastic lesions.There was an increase in hepatic adenomas and carcinomas in males, and hepatic carcinomas in females at 500 mg/kg/day. Systemic exposure in rats at 150 and 500 mg/kg/day are 19 and 58 times, respectively, that of humans at 100 mg/day. The no-observed effect level for induction of hepatic neoplasia in rats was 150 mg/kg/day, producing exposure approximately 19-fold higher than the human exposure at the 100mg/day clinical dose . The increased incidence of hepatic tumours was likely secondary to chronic hepatic toxicity at this high dose. The clinical significance of these findings for humans is unknown.

In a two-year carcinogenicity study conducted in mice, sitagliptin did not increase tumour incidence at oral doses up to 500 mg/kg/day (approximately 68 times human exposure at the clinical dose of 100 mg/day).

Genotoxicity

Sitagliptin was not mutagenic or clastogenic in a battery of genetic toxicology studies, including the Ames bacterial mutagenicity assay, a chromosome aberration assay in Chinese hamster ovary cells, an *in vitro* rat hepatocyte DNA alkaline elution assay (an assay which measures the compound's ability to induce single strand breaks in DNA), and an *in vivo* mouse micronucleus assay.

Interactions with other medicines

***In vitro* Assessment of Drug Interactions:**

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6 and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilise these pathways.

Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

***In Vivo* Assessment of Drug Interactions:**

Effects of Sitagliptin on Other Drugs

In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Multiple doses of sitagliptin slightly increased digoxin concentrations; however, these increases are not considered likely to be clinically meaningful and are not attributed to a specific mechanism.

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

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

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

Thiazolidinediones: Single-dose pharmacokinetics of rosiglitazone were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP2C8-mediated metabolism. Clinically meaningful interactions with pioglitazone are not expected because pioglitazone predominantly undergoes CYP2C8- or CYP3A4-mediated metabolism.
Warfarin: Multiple daily doses of sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Since S(-) warfarin is primarily metabolised by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.

Oral Contraceptives: Co-administration with sitagliptin did not meaningfully alter the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of JANUVIA daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma C_{max} by 18%. These increases are not considered to be clinically meaningful.

Effects of Other Drugs on Sitagliptin
Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by co-administered medications:

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

Cyclosporin: A study was conducted to assess the effect of cyclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Coadministration of a single 100-mg oral dose of JANUVIA and a single 600-mg oral dose of cyclosporin increased the AUC and C_{max} of sitagliptin by approximately 29% and 68%, respectively. These modest changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Population Pharmacokinetics: 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, but not restricted to, cholesterol-lowering agents (including statins, fibrates, ezetimibe), anti-platelet agents (including clopidogrel), antihypertensives (including ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (including naproxen, diclofenac, celecoxib), anti-depressants (including bupropion, fluoxetine, sertraline), antihistamines (including cetirizine), proton-pump inhibitors (including omeprazole, lansoprazole), and medications for erectile dysfunction (including sildenafil).

Use with other antidiabetic agents:
The safety and efficacy of sitagliptin in combination with insulin, GLP-1 mimetics, or alpha-glucosidase inhibitors has not been established.

Other Drugs:
Sitagliptin has not been studied in combination with orlistat.

ADVERSE REACTIONS

In controlled clinical studies as both monotherapy and combination therapy with metformin or pioglitazone, the overall incidence of adverse reactions, hypoglycaemia, and discontinuation of therapy due to clinical adverse reactions with JANUVIA were similar to placebo. In combination with glimepiride, with or without metformin, the overall incidence of clinical adverse reactions with JANUVIA was higher than with placebo, in part related to a higher incidence of hypoglycaemia (see Table 6); the incidence of discontinuation due to clinical adverse reactions was similar to placebo.

Two placebo-controlled monotherapy studies, one of 18- and one of 24-week duration, included patients treated with JANUVIA 100 mg daily, JANUVIA 200 mg daily, and placebo. Three 24-week, placebo-controlled add-on combination therapy studies, one with metformin, one with pioglitazone, and one with glimepiride with or without metformin, were also conducted. In addition to a stable dose of metformin, pioglitazone, glimepiride, or glimepiride and metformin, patients whose diabetes was not adequately controlled were given either JANUVIA 100 mg daily or placebo. The adverse reactions, reported regardless of investigator assessment of causality in ³ 5% of patients treated with JANUVIA 100 mg daily as monotherapy, JANUVIA in combination with pioglitazone, or JANUVIA in combination with glimepiride, with or without metformin, and more commonly than in patients treated with placebo, are shown in Table 6.

Table 6
Placebo-Controlled Clinical Studies of JANUVIA Monotherapy* or Add-on Combination Therapy with Pioglitazone or Glimepiride +/- Metformin: Adverse Reactions Reported in ³ 5% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality†

Body System/Adverse Reactions	Number of Patients (%)	
	JANUVIA 100 mg	**Placebo**
	N = 443	N = 363
Infections and Infestations		
Nasopharyngitis	23 (5.2)	12 (3.3)
	JANUVIA 100 mg + Pioglitazone	**Placebo + Pioglitazone**
	N = 175	N = 178
Infections and Infestations		
Upper Respiratory Tract Infection	11 (6.3)	6 (3.4)
Nervous System Disorders		
Headache	9 (5.1)	7 (3.9)
	JANUVIA 100 mg + Glimepiride (+/- Metformin)	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Metabolism and Nutrition disorders		
Hypoglycaemia	27 (12.2)	4 (1.8)
Infections and Infestations		
Nasopharyngitis	14 (6.3)	10 (4.6)
Nervous System Disorders		

Headache	13 (5.9)	5 (2.3)

† Intent to treat population
*Overall, the safety profile of the 200-mg daily dose was similar to that of the 100-mg daily dose.

In an additional, 24-week, placebo-controlled factorial study of initial therapy with sitagliptin in combination with metformin, the adverse reactions reported (regardless of investigator assessment of causality) in ³ 5% of patients are shown in Table 7.

Table 7
Initial Therapy with Combination of Sitagliptin and Metformin:
Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ³ 5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)†

	Number of Patients (%)			
	Placebo/ Metformin 1000 mg bid	**Sitagliptin (JANUVIA) 100 mg QD**	**Metformin 500 or 1000 mg bid ††**	**Sitagliptin 50 mg bid + Metformin 500 or 1000 mg bid ††**
	N = 176	N = 179	N = 364††	N = 372††
Diarrhoea	12 (6.8)	8 (4.5)	37 (10.1)	44 (11.8)
Nausea	4 (2.3)	2 (1.1)	25 (6.9)	22 (5.9)
Bronchitis	8 (4.5)	3 (1.7)	14 (3.8)	27 (7.3)
Influenza	5 (2.8)	8 (4.5)	25 (6.9)	20 (5.4)
Upper Respiratory Tract Infection	13 (7.4)	12 (6.7)	37 (10.2)	45 (12.1)
Urinary Tract Infection	4 (2.3)	0 (0)	21 (5.8)	19 (5.1)
Arthralgia	3 (1.7)	7 (3.9)	18 (4.9)	20 (5.4)
Back Pain	9 (5.1)	9 (5.0)	16 (4.4)	24 (6.5)
Headache	7 (4.0)	6 (3.4)	21 (5.8)	27 (7.3)

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

Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. The overall incidence of pre-specified adverse reactions of hypoglycemia in patients with type 2 diabetes inadequately controlled on diet and exercise was 2.8% in patients given placebo, 1.1% in patients given sitagliptin alone, 1.9% in patients given metformin alone, and 3.8% in patients given sitagliptin in combination with metformin.
No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with JANUVIA.

Treatment-emergent adverse events were reported in similar numbers across all treatment groups. Over the two-year treatment period, discontinuation due to loss of efficacy was reported more commonly in the 100 mg sitagliptin group than other treatment groups.

Table 8: Initial Therapy with Sitagliptin or Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ³ 5% of Patients Receiving Mono Therapy all patients "as treated"

	Number of patients(%)	
	Sitagliptin	**Metformin**
	N = 528	**N = 522**
Diarrhoea	**19 (3.6)**	**57 (10.9)**

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

In the pre specified pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the overall incidence of adverse experiences of hypoglycaemia in patients treated with JANUVIA 100 mg was similar to placebo (1.2% vs. 0.9%). Adverse experiences of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The incidence of selected gastrointestinal adverse reactions in patients treated with JANUVIA or placebo was as follows: abdominal pain (JANUVIA, 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), vomiting (0.8%, 0.9%), and diarrhoea (3.0%, 2.3%).

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

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.

Postmarketing Experience

Additional adverse reactions have been identified during postmarketing use of JANUVIA as monotherapy and/or in combination with other antihyperglycaemic 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 haemorrhagic and necrotising pancreatitis (see **PRECAUTIONS**, *Pancreatitis*); worsening renal function, including acute renal failure (sometimes requiring dialysis); constipation; vomiting; headache; arthralgia; myalgia; pain in extremity; back pain.

DOSAGE AND ADMINISTRATION

The recommended dose of JANUVIA is 100 mg once daily as monotherapy, or as combination therapy with metformin, or a sulfonylurea (clinical experience is with glimepiride as dual therapy), or a thiazolidinedione (clinical experience is with pioglitazone as dual therapy). JANUVIA can be taken with or without food.

When JANUVIA is used in combination with a sulfonylurea, reduction in the dose of sulfonylurea may be considered to reduce the risk of sulfonylurea-induced hypoglycaemia (see **PRECAUTIONS**, *Hypoglycaemia in Combination with a Sulfonylurea*).

Patients with Renal Insufficiency

For patients with mild renal insufficiency (creatinine clearance [CrCl] ³ 50 mL/min, approximately corresponding to serum creatinine levels of £150micromol/L in men and £133 micromol/L in women), no dosage adjustment for JANUVIA is required.

For patients with moderate renal insufficiency (CrCl ³ 30 to <50 mL/min, approximately corresponding to serum creatinine levels of >150 to £265 micromol/L in men and >133 to £221 micromol/L in women), the dose of JANUVIA is 50 mg once daily.

For patients with severe renal insufficiency (CrCl <30 mL/min, approximately corresponding to serum creatinine levels of >265 micromol/L in men and >221 micromol/L in women) or with end-stage renal disease (ESRD) requiring haemodialysis or peritoneal dialysis, the dose of JANUVIA is 25 mg once daily. JANUVIA may be administered without regard to the timing of haemodialysis.

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

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 **PHARMACOLOGY**, **Pharmacodynamics**, ***Cardiac Electrophysiology***). There is no experience with doses above 800 mg in humans. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with JANUVIA with doses of up to 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 dialysable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE

JANUVIA is available in the following presentations:

JANUVIA Tablet 25 mg - A pink, round, film coated tablet with ”221” on one side and plain on the other. Available in blister packs of 28 tablets.

JANUVIA Tablet 50 mg - A light beige, round, film coated tablet with ”112” on one side and plain on the other. Available in blister packs of 28 tablets.

JANUVIA Tablet 100 mg - A beige, round, film coated tablet with ”277” on one side and plain on the other. Available in blister packs of 7 (Starter Pack) and 28 tablets.

Store below 30°C. Store in original packaging.

NAME AND ADDRESS OF SPONSOR

MERCK SHARP & DOHME (AUSTRALIA) PTY LIMITED
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SOUTH GRANVILLE NSW 2142

POISON SCHEDULE

Prescription Only Medicine (Schedule 4)

This document was approved by the Therapeutic Goods Administration on 21st December 2007. Date of most recent amendment 05 September 2012.