JANUVIA™

25/50/100 mg Tablets

(Sitagliptin 25/50/100 mg)

INDICATIONS AND USAGE

- **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 or PPARγ agonist**

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

- **Combination with Metformin and Sulfonylurea**

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

- **Combination with Insulin**

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

When Januvia is used in combination with a sulfonylurea or with insulin, a lower dose of the sulfonylurea or insulin may be considered to reduce the risk of hypoglycemia.

DOSAGE AND ADMINISTRATION

Recommended Dosing

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

When used in combination with metformin or a PPARγ agonist, the dose of metformin or PPARγ agonist should be maintained, and Januvia administered concomitantly.

When Januvia is used in combination with a sulfonylurea or with insulin, a lower dose of the sulfonylurea or insulin may be considered to reduce the risk of

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hypoglycaemia

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 (JANUVIA 25 mg is not marketed in Indonesia).

Pediatric Patients

Januvia is not indicated in pediatric patients 10 to 17 years old with type 2 diabetes. Januvia has not been studied in pediatric patients under 10 years of age.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis (see ADVERSE REACTIONS), in patients taking JANUVIA. After initiation of JANUVIA, patients should be observed carefully for signs and symptoms of pancreatitis. 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

A dosage adjustment is 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]*

Use with Medications Known to Cause Hypoglycemia

As is typical with other antihyperglycemic agents, hypoglycemia has been observed when JANUVIA was used in combination with insulin or a sulfonylurea. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

Macrovascular Outcomes

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

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.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled clinical studies as both monotherapy and combination therapy with metformin, pioglitazone, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to clinical adverse reactions with JANUVIA was also 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 hypoglycemia (see Table 1); 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. Five placebo-controlled add-on combination therapy studies were also conducted, one with metformin; one with pioglitazone; one with metformin and rosiglitazone; one with glimepiride (with or without metformin); and one with insulin (with or without metformin). In these trials, patients with inadequate glycemic control on a stable dose of the background therapy were randomized to add-on therapy with JANUVIA 100 mg daily or placebo. The adverse reactions, excluding hypoglycemia, reported regardless of investigator assessment of causality in ≥5% of patients treated with JANUVIA 100 mg daily and more commonly than in patients treated with placebo, are shown in Table 1 for the clinical trials of at least 18 weeks duration. Incidence of hypoglycemia are shown in Table 2.

Table 1

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

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

Headache	13 (5.9)	5 (2.3)

† Intent to treat population

In the 24-week study of patients receiving 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 24-week study of patients receiving JANUVIA as add-on therapy to stable-dose insulin (with or without metformin), there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo, except for hypoglycemia (see Table 2). 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. In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the incidence of selected gastrointestinal adverse reactions in patients treated with JANUVIA was as follows: abdominal pain (JANUVIA 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), and diarrhea (3.0%, 2.3%).

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

Hypoglycemia

In all (N=9) studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia. A concurrent blood glucose measurement was not required although most (74%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL. When JANUVIA was co-administered with a sulfonylurea or with insulin, the percentage of patients with at least one adverse reaction of hypoglycemia was higher than in the corresponding placebo group (Table 2).

Table 2

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

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

† Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required; intent-to-treat population.

‡ Based on total number of events (i.e., a single patient may have had multiple events).

§ Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

In a 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 reactions of hypoglycemia was 1.2% in patients treated with JANUVIA 100 mg and 0.9% in patients treated with placebo.

TECOS Cardiovascular Safety Study.

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline estimated glomerular filtration rate (eGFR) was ≥30 and <50 mL/min/1.73 m^2), and 7,339 patients

treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA_{1c} and CV risk factors. The study population included a total of 2,004 patients ≥75 years of age (970 treated with sitagliptin and 1,034 treated with placebo). The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo. Assessment of pre-specified diabetes-related complications revealed similar incidences between groups including infections (18.4% of the sitagliptin -treated patients and 17.7% of the placebo-treated patients) and renal failure (1.4% of sitagliptin-treated patients and 1.5% of placebo-treated patients). The adverse event profile in patients ≥75 years of age was generally similar to the overall population.

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

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

Laboratory Tests

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

and in patients treated with placebo [0.07 mg/dL (0.07)]. The clinical significance of this added increase in serum creatinine relative to placebo is not known.

Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of 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 Warnings and Precautions]*; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis *[Warnings and Precautions]*; constipation; vomiting; headache, worsening renal function, including acute renal failure (sometimes requiring dialysis), bullous pemphigoid (see WARNINGS AND PRECAUTIONS, Bullous Pemphigoid); arthralgia, myalgia, pain in extremity, back pain, pruritus.

DRUG INTERACTIONS

Digoxin

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 100 mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or JANUVIA is recommended.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to

20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30- and 20-times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

Nursing Mothers

Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUVIA is administered to a nursing woman.

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.

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

Geriatric Use

Of the total number of subjects (N=3884) in clinical safety and efficacy studies of JANUVIA, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical

experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly, and it may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter *[see Dosage and Administration, Patients with Renal impairment, Clinical Pharmacology, Pharmacokinetics]*.

OVERDOSAGE

During controlled clinical trials in healthy subjects, single doses of up to 800 mg JANUVIA were administered. Maximal mean increases in QTc of 8.0 msec were observed in one study at a dose of 800 mg JANUVIA, a mean effect that is not considered clinically important *[see Clinical Pharmacology, Pharmacodynamics]*. There is no experience with doses above 800 mg in humans.

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

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

CLINICAL PHARMACOLOGY

Mechanism of Action

Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by JANUVIA, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling

pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, JANUVIA increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity *in vitro* at concentrations approximating those from therapeutic doses.

Pharmacodynamics

General

In patients with type 2 diabetes, administration of JANUVIA led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

In studies with healthy subjects, JANUVIA did not lower blood glucose or cause hypoglycemia.

Cardiac Electrophysiology

In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of 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 was observed at 3 hours postdose and was 8.0 msec. This increase is not considered to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11-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.

Pharmacokinetics

The pharmacokinetics of sitagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100 mg dose to

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

Absorption

The absolute bioavailability of sitagliptin is approximately 87%. Because coadministration of a high-fat meal with 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 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Metabolism

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

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

Excretion

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

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

a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Special Populations

Renal Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of 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 ≥ 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2) and patients with moderate renal impairment (eGFR ≥ 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2), respectively. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2), and approximately 4-fold in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), including patients with ESRD on hemodialysis. Sitagliptin was modestly removed by hemodialysis (13.5% over a 3- to 4-hour hemodialysis session starting 4 hours 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).

Body Mass Index (BMI)

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

Gender

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

Geriatric

No dosage adjustment is required based solely on age. When the effects of age on renal function are taken into account, age alone did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Pediatric

The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in pediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18% lower compared to adult patients with type 2 diabetes for a 100 mg dose. This is not considered to be a clinically meaningful difference based on the flat PK/PD relationship between the dose of 50 mg and 100 mg in adults.

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

Race

No dosage adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of available pharmacokinetic data, including subjects of white, Hispanic, black, Asian, and other racial groups.

Drug Interactions

In Vitro Assessment of Drug Interactions

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but

does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways.

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

In Vivo Assessment of Drug Interactions

Effects of Sitagliptin on Other Drugs

In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT).

Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of JANUVIA daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma C_{max} by 18%.

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

Sulfonylureas: Single-dose pharmacokinetics of glyburide, a CYP2C9 substrate, was not meaningfully altered in subjects receiving multiple doses of sitagliptin. Clinically meaningful interactions would not be expected with other sulfonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glyburide, are primarily eliminated by CYP2C9. However, the risk of hypoglycemia from the co-administration of sitagliptin and sulfonylureas is unknown.

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

Warfarin: Multiple daily doses of sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Because S(-) warfarin is primarily metabolized by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.

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

Effects of Other Drugs on Sitagliptin

Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by co-administered medications:

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

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination

(approximately 8 weeks total) and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, nondose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison).

CLINICAL STUDIES

There were approximately 5200 patients with type 2 diabetes randomized in nine double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of sitagliptin on glycemic control. In these studies, the mean age of patients was 54.8 years, and 62% of patients were white, 18% were Hispanic, 6% were black, 9% were Asian, and 4% were of other racial groups.

In patients with type 2 diabetes, treatment with JANUVIA produced clinically significant improvements in hemoglobin A_{1C}, fasting plasma glucose (FPG) and 2-hour post-prandial glucose (PPG) compared to placebo.

Monotherapy

A total of 1262 patients with type 2 diabetes participated in two double-blind, placebo-controlled studies, one of 18-week and another of 24-week duration, to evaluate the efficacy and safety of JANUVIA monotherapy. In both monotherapy studies, patients currently on an antihyperglycemic agent discontinued the agent, and underwent a diet, exercise, and drug wash-out period of about 7 weeks. Patients with inadequate glycemic control (A_{1C} 7% to 10%) after the wash-out period were randomized after completing a 2-week single-blind placebo run-in period; patients not currently on antihyperglycemic agents (off therapy for at least 8 weeks) with inadequate glycemic control (A_{1C} 7% to 10%) were randomized after completing the 2-week single-blind placebo run-in period. In the 18-week study, 521 patients were randomized to placebo, JANUVIA 100 mg, or JANUVIA 200 mg, and in the 24-week study 741 patients were randomized to placebo, JANUVIA 100 mg, or JANUVIA 200 mg. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue, added on to placebo or JANUVIA.

Treatment with JANUVIA at 100 mg daily provided significant improvements in A_{1C}, FPG, and 2-hour PPG compared to placebo (Table 3). In the 18-week study, 9% of patients receiving JANUVIA 100 mg and 17% who received placebo required rescue

therapy. In the 24-week study, 9% of patients receiving JANUVIA 100 mg and 21% of patients receiving placebo required rescue therapy. The improvement in A_{1C} was not affected by gender, age, race, or baseline BMI. As is typical for trials of agents to treat type 2 diabetes, mean response to JANUVIA in A_{1C} lowering appears to be related to the degree of A_{1C} elevation at baseline. 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 3

Glycemic 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
A1C (%)	**N = 193**	**N = 103**	**N = 229**	**N = 244**
Baseline (mean)	8.0	8.1	8.0	8.0
Change from baseline (adjusted mean‡)	-0.5	0.1	-0.6	0.2
Difference from placebo (adjusted mean‡) (95% CI)	-0.6§ (-0.8, -0.4)		-0.8§ (-1.0, -0.6)	
Patients (%) achieving A1C <7%	69 (36%)	16 (16%)	93 (41%)	41 (17%)
FPG (mg/dL)	**N = 201**	**N = 107**	**N = 234**	**N = 247**
Baseline (mean)	180	184	170	176
Change from baseline (adjusted mean‡)	-13	7	-12	5
Difference from placebo (adjusted mean‡) (95% CI)	-20§ (-31, -9)		-17§ (-24, -10)	
2-hour PPG (mg/dL)	%	%	**N = 201**	**N = 204**
Baseline (mean)			257	271
Change from baseline (adjusted mean‡)			-49	-2
Difference from placebo (adjusted mean‡) (95% CI)			-47§ (-59, -34)	

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

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

§ p<0.001 compared to placebo

‖ Data not available

Additional Monotherapy Study

A multinational, randomized, double-blind, placebo-controlled study was also conducted to assess the safety and tolerability of 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. A small increase in serum creatinine was reported in patients with moderate renal insufficiency treated with JANUVIA relative to those on placebo. In addition, the reductions in A1C and FPG with JANUVIA compared to placebo were generally similar to those observed in other monotherapy studies. *(See Clinical Pharmacology,* Pharmacokinetics, *Special Populations, Renal Impairment*.)

Combination Therapy

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. Patients already on metformin (N=431) at a dose of at least 1500 mg per day were randomized after completing a 2-week single-blind placebo run-in period. Patients on metformin and another antihyperglycemic agent (N=229) and patients not on any antihyperglycemic agents (off therapy for at least 8 weeks, N=41) were randomized after a run-in period of approximately 10 weeks on metformin (at a dose of at least 1500 mg per day) in monotherapy. Patients were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

In combination with metformin, JANUVIA provided significant improvements in A_{1C}, FPG, and 2-hour PPG compared to placebo with metformin (Table 4). Rescue glycemic therapy was used in 5% of patients treated with JANUVIA 100 mg and 14% of patients treated with placebo. A similar decrease in body weight was observed for both treatment

groups.

Table 4

Glycemic Parameters at Final Visit (24-Week Study) for JANUVIA in Combination with Metformin†

	JANUVIA 100 mg + Metformin	Placebo + Metformin
A1C (%)	**N = 453**	**N = 224**
Baseline (mean)	8.0	8.0
Change from baseline (adjusted mean‡)	-0.7	-0.0
Difference from placebo + metformin (adjusted mean‡) (95% CI)	-0.7§ (-0.8, -0.5)	
Patients (%) achieving A1C <7%	213 (47%)	41 (18%)
FPG (mg/dL)	**N = 454**	**N = 226**
Baseline (mean)	170	174
Change from baseline (adjusted mean‡)	-17	9
Difference from placebo + metformin (adjusted mean‡) (95% CI)	-25§ (-31, -20)	
2-hour PPG (mg/dL)	**N = 387**	**N = 182**
Baseline (mean)	275	272
Change from baseline (adjusted mean‡)	-62	-11
Difference from placebo + metformin (adjusted mean‡) (95% CI)	-51§ (-61, -41)	

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

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

§ $p<0.001$ compared to placebo + metformin

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. Patients on any oral antihyperglycemic agent in monotherapy (N=212) or on a PPARγ agent in combination therapy (N=106) or not on an antihyperglycemic agent (off therapy for at least 8 weeks, N=34) were switched to monotherapy with pioglitazone (at a dose of 30-45 mg per day), and completed a run-in period of approximately 12 weeks in duration. After the run-in period on pioglitazone

monotherapy, patients were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue. Glycemic endpoints measured included A_{1C} and fasting glucose.

In combination with pioglitazone, JANUVIA provided significant improvements in A_{1C} and FPG compared to placebo with pioglitazone (Table 5). Rescue therapy was used in 7% of patients treated with JANUVIA 100 mg and 14% of patients treated with placebo. There was no significant difference between JANUVIA and placebo in body weight change.

Table 5

Glycemic Parameters at Final Visit (24-Week Study) for JANUVIA in Combination with Pioglitazone†

	JANUVIA 100 mg + Pioglitazone	Placebo + Pioglitazone
A1C (%)	**N = 163**	**N = 174**
Baseline (mean)	8.1	8.0
Change from baseline (adjusted mean‡)	-0.9	-0.2
Difference from placebo + pioglitazone (adjusted mean‡) (95% CI)	-0.7§ (-0.9, -0.5)	
Patients (%) achieving A1C <7%	74 (45%)	40 (23%)
FPG (mg/dL)	**N = 163**	**N = 174**
Baseline (mean)	168	166
Change from baseline (adjusted mean‡)	-17	1
Difference from placebo + pioglitazone (adjusted mean‡) (95% CI)	-18§ (-24, -11)	

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

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

§ p<0.001 compared to placebo + pioglitazone.

Add-on Combination Therapy with Glimepiride and Metformin

A total of 229 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 with metformin. Patients entered a run-in treatment period

on glimepiride (≥4 mg per day) in combination with metformin (≥1500 mg per day). After a dose-titration and dose-stable run-in period of up to 16 weeks and a 2-week placebo run-in period, patients with inadequate glycemic control (A_{1C} 7.5% to 10.5%) were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

Patients receiving sitagliptin with metformin and glimepiride had significant improvements in A_{1C} and FPG compared to patients receiving placebo with metformin and glimepiride (Table 6), with mean reductions from baseline relative to placebo in A_{1C} of -0.9% and in FPG of -21 mg/dL. Rescue therapy was used in 8% of patients treated with add-on sitagliptin 100 mg and 29% of patients treated with add-on placebo. The patients treated with add-on sitagliptin had a mean increase in body weight of 1.1 kg vs. add-on placebo (+0.4 kg vs. -0.7 kg). In addition, add-on sitagliptin resulted in an increased rate of hypoglycemia compared to add-on placebo.

Table 6: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin in Combination with Metformin and Glimepiride†

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

† Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy.

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

§ p<0.001 compared to placebo.

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). The racial distribution in this study was approximately 70% white, 18% Asian, 7% black, and 5% other groups. Approximately 14% of the patients in this study were Hispanic. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin (≥1500 mg per day). Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a pre-mixed insulin. After the run-in period, patients with inadequate glycemic control (A_{1C} 7.5% to 11%) were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Patients were on a stable dose of insulin prior to enrollment with no changes in insulin dose permitted during the run-in period. Patients who failed to meet specific glycemic goals during the double-blind treatment period were to have uptitration of the background insulin dose as rescue therapy.

The median daily insulin dose at baseline was 42 units in the patients treated with JANUVIA and 45 units in the placebo-treated patients. The median change from baseline in daily dose of insulin was zero for both groups at the end of the study. In combination with insulin (with or without metformin), JANUVIA provided significant improvements in A_{1C}, FPG, and 2-hour PPG compared to placebo (Table 7). Both treatment groups had an adjusted mean increase in body weight of 0.1 kg from baseline to Week 24. There was an increased rate of hypoglycemia in patients treated with JANUVIA. *[See Warnings and Precautions; Adverse Reactions.]*

Table 7

Glycemic Parameters at Final Visit (24-Week Study) for JANUVIA as Add-on Combination Therapy with Insulin†

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

† Intent-to-treat population using last observation on study prior to rescue therapy.

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

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

‖ p<0.001 compared to placebo.

In another 24-week, randomized, double-blind, placebo-controlled study designed to assess the insulin-sparing efficacy of 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 sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥30 and <50 mL/min/1.73 m^2) or placebo (7,339) added to usual care targeting regional standards for HbA_{1c} and CV risk factors. Patients with an eGFR <30 mL/min/1.73 m^2 were not to be enrolled in the study. The study population included 2,004 patients ≥75 years of age and 3,324 patients with renal impairment (eGFR <60 mL/min/1.73 m^2).

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

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

occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.

After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalization for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes (Table 8).

Table 8

Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	SITAGLIPTIN 100 mg		Placebo			
	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, nonfatal myocardial infarction, nonfatal 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, nonfatal myocardial infarction, or nonfatal 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, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2	0.98 (0.89–1.08)	<0.001
Secondary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)	745 (10.2)	3.6	746 (10.2)	3.6	0.99 (0.89–1.10)	<0.001
Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89-1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81–1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79–1.19)	0.760
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.

HOW SUPPLIED/STORAGE AND HANDLING

JANUVIA 50 Box, 2 blisters @ 14 tablets – Reg. No.: DKL2106609817A1

JANUVIA 100 Box, 2 blisters @ 14 tablets – Reg. No.: DKL2106609817B1

Storage

Store below 30°C

HARUS DENGAN RESEP DOKTER

Manufactured by:

Organon Pharma (UK) Limited

Shotton Lane, Cramlington

Northumberland NE23 3JU, England

Registered and packed by:

PT Organon Pharma Indonesia Tbk

Pasuruan, Jawa Timur

Distributed by:

PT Merck Sharp & Dohme Indonesia

Jakarta, Indonesia

USPI (240910), WPC-MK0431-T-052020

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INFORMASI MENGENAI JANUVIA UNTUK PASIEN

Bacalah lembar informasi ini dengan seksama sebelum anda mulai menggunakan obat, meskipun anda pernah menggunakan obat ini sebelumnya. Beberapa informasi dapat saja berubah.

Ingatlah bahwa dokter anda meresepkan obat ini hanya untuk anda. Jangan pernah memberikan obat anda kepada orang lain.

Apakah JANUVIA?

JANUVIA (sitagliptin phosphate, MSD) adalah tablet yang mengandung 50 atau 100 mg sitagliptin sebagai bahan aktif.

Selain itu, JANUVIA mengandung zat tambahan berikut: *Microcrystalline Cellulose, Dibasic Calcium Phosphate, Croscarmellose Sodium, Magnesium Stearate, Sodium Stearyl Fumarate, Purified water, Opadry® II.*

JANUVIA adalah anggota kelas obat-obatan yang digunakan secara oral melalui mulut yang disebut inhibitor DPP-4 (dipeptidyl peptidase-4 inhibitor) yang menurunkan kadar gula darah pada pasien dengan diabetes mellitus tipe 2. Diabetes tipe 2 juga disebut *Non-Insulin-Dependent Diabetes Melitus*, atau NIDDM.

- JANUVIA membantu meningkatkan kadar insulin setelah makan.
- JANUVIA menurunkan jumlah gula yang dibuat oleh tubuh.
- JANUVIA bekerja ketika gula darah tinggi, terutama setelah makan. Ini adalah ketika tubuh membutuhkan bantuan terbesar dalam menurunkan gula darah. JANUVIA juga menurunkan gula darah di antara waktu makan.
- JANUVIA sendiri tidak mungkin menyebabkan gula darah rendah (hipoglikemia) karena tidak bekerja ketika gula darah Anda rendah.

Didaftarkan oleh:

PT Organon Pharma Indonesia Tbk
Pasuruan, Jawa Timur

DISETUJUI OLEH BPOM : 29/10/2021

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EREG100373VR12100478

Didistribusikan oleh:

PT Merck Sharp & Dohme Indonesia

Jakarta, Indonesia

Produsen pembuat produk:

Organon Pharma (UK) Limited,

Shotton Lane, Cramlington,

Northumberland NE23 3JU, England

Mengapa dokter saya meresepkan JANUVIA?

Dokter Anda telah meresepkan JANUVIA untuk membantu menurunkan gula darah Anda yang terlalu tinggi karena diabetes tipe 2 Anda. JANUVIA dapat digunakan sendiri atau dikombinasikan dengan obat-obatan tertentu lainnya yang menurunkan gula darah, bersama dengan program diet dan olahraga yang disarankan.

Apa itu diabetes tipe 2?

Diabetes tipe 2 adalah suatu kondisi di mana tubuh Anda tidak menghasilkan cukup insulin, dan insulin yang diproduksi oleh tubuh Anda tidak berfungsi sebagaimana mestinya. Tubuh Anda juga bisa membuat terlalu banyak gula. Ketika ini terjadi, gula (glukosa) menumpuk di dalam darah. Ini dapat menyebabkan masalah medis yang serius.

Tujuan utama mengobati diabetes adalah menurunkan gula darah Anda ke tingkat normal. Menurunkan dan mengendalikan gula darah dapat membantu mencegah atau menunda komplikasi diabetes, seperti penyakit jantung, penyakit ginjal, kebutaan, dan amputasi.

Gula darah tinggi dapat diturunkan dengan diet dan olahraga, dan dengan obat-obatan tertentu.

Apa yang sebaiknya saya ketahui sebelum dan saat menggunakan JANUVIA ?

Siapa yang tidak boleh menggunakan JANUVIA?

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Jangan mengambil JANUVIA jika Anda alergi terhadap salah satu bahan di JANUVIA.

Apa yang harus saya sampaikan kepada dokter saya sebelum menggunakan JANUVIA?

Katakan kepada dokter Anda jika Anda memiliki atau pernah:

- diabetes tipe 1
- ketoasidosis diabetik (peningkatan keton dalam darah atau urine)
- masalah ginjal apa saja, atau masalah medis sebelumnya atau yang ada
- reaksi alergi terhadap JANUVIA

Ketika menggunakan JANUVIA

Kasus-kasus peradangan pankreas (pankreatitis) telah dilaporkan pada pasien yang menerima JANUVIA. Pankreatitis bisa menjadi kondisi medis yang serius dan berpotensi mengancam nyawa. Berhenti minum JANUVIA dan hubungi dokter Anda jika Anda mengalami sakit perut yang parah dan terus-menerus, dengan atau tanpa muntah, karena Anda bisa menderita pankreatitis.

Kasus-kasus dari suatu reaksi kulit yang disebut *bullous pemphigoid* yang dapat memerlukan perawatan di rumah sakit telah dilaporkan pada pasien yang menerima JANUVIA. Katakan kepada dokter Anda jika Anda mengalami kulit melepuh atau kerusakan kulit Anda (erosi). Dokter Anda mungkin meminta Anda untuk berhenti mengambil JANUVIA.

Penggunaan pada anak-anak

JANUVIA tidak efektif pada anak-anak dan remaja usia 10 hingga 17 tahun dengan diabetes tipe 2. JANUVIA belum diteliti pada anak di bawah 10 tahun.

Penggunaan pada lanjut usia

Dalam penelitian, JANUVIA bekerja dengan baik dan ditoleransi dengan baik oleh pasien dewasa yang lebih tua. Tidak diperlukan penyesuaian dosis berdasarkan usia.

Penggunaan pada wanita hamil dan menyusui

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Wanita yang hamil atau berencana untuk hamil harus berkonsultasi dengan dokter mereka sebelum mengambil JANUVIA. JANUVIA tidak direkomendasikan untuk digunakan selama kehamilan.

Tidak diketahui apakah JANUVIA dapat tersalurkan ke ASI. Anda tidak boleh menggunakan JANUVIA jika Anda menyusui atau berencana untuk menyusui.

Dapatkah saya menggunakan JANUVIA bersamaan dengan obat-obatan lain?

JANUVIA dapat diminum dengan sebagian besar obat-obatan. Katakan kepada dokter Anda tentang semua obat yang Anda gunakan. Termasuk obat resep dan non-resep, dan suplemen herbal.

Dapatkah saya mengendarai kendaraan atau mengoperasikan mesin ketika saya menggunakan JANUVIA?

Belum ada informasi tentang pengaruh JANUVIA terhadap kemampuan dalam berkendara dan mengoperasikan mesin.

Bagaimana saya menggunakan JANUVIA?

Gunakan JANUVIA persis seperti yang diresepkan dokter Anda. Dosis yang dianjurkan adalah:

- satu tablet 100 mg
- sekali sehari
- secara oral melalui mulut, dengan atau tanpa makanan

Jika Anda memiliki masalah ginjal, dokter Anda mungkin akan meresepkan dosis yang lebih rendah.

Dokter Anda mungkin meresepkan JANUVIA bersama dengan obat-obatan tertentu lainnya yang menurunkan gula darah.

Lanjutkan untuk menggunakan JANUVIA selama dokter meresepkannya sehingga Anda dapat terus membantu mengontrol gula darah Anda.

Diet dan olahraga dapat membantu tubuh Anda menggunakan gula darah dengan lebih baik.

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Minum JANUVIA hanya ketika diresepkan oleh dokter. Ikuti semua petunjuk yang diberikan oleh dokter untuk Anda. Jika Anda tidak mengerti pada instruksi yang terdapat pada kemasan, tanyakan pada dokter atau apoteker untuk membantu anda. Penting untuk tetap mengikuti program diet, olahraga, dan penurunan berat badan yang dianjurkan dokter Anda saat mengambil JANUVIA.

Apa yang harus saya lakukan pada kejadian overdosis?

Jika anda mengkonsumsi JANUVIA secara berlebihan, segera hubungi dokter.

Apa yang harus saya lakukan apabila saya melewatkan satu dosis?

Jika anda melewatkan satu dosis, minumlah dosis tersebut segera setelah anda mengingatnya. Apabila anda tidak mengingatnya sampai waktu dosis berikutnya, lewati dosis tersebut dan kembalilah pada jadwal regular anda. Jangan menggunakan dosis ganda JANUVIA.

Apa saja efek yang tidak diinginkan yang dapat disebabkan oleh JANUVIA?

Seperti semua obat resep, JANUVIA dapat menyebabkan efek samping. Dalam penelitian, efek samping biasanya ringan dan tidak menyebabkan pasien berhenti menggunakan JANUVIA. Efek samping yang dilaporkan pada pasien yang diobati dengan JANUVIA mirip dengan efek samping pada pasien yang diobati dengan tablet yang tidak mengandung obat (plasebo).

Ketika JANUVIA digunakan dalam kombinasi dengan obat sulfonilurea atau dengan insulin, gula darah rendah dengan gejala (hipoglikemia) karena sulfonilurea atau insulin dapat terjadi. Dosis rendah obat sulfonilurea atau insulin mungkin diperlukan.

Ketika JANUVIA digunakan dalam kombinasi dengan insulin, efek samping tambahan berikut dilaporkan:

- Flu
- Sakit kepala

Ketika JANUVIA dan metformin digunakan bersama, efek samping berikut dilaporkan:

- Diare
- Gangguan pencernaan

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- Perut kembung
- Muntah
- Sakit kepala

Ketika JANUVIA dan pioglitazone dimulai bersama-sama, efek samping dari penurunan pengukuran gula darah tanpa gejala hipoglikemia dilaporkan.

Ketika JANUVIA digunakan dalam kombinasi dengan metformin dan rosiglitazone, efek samping berikut dilaporkan:

- Sakit kepala
- Gula darah rendah dengan gejala (hipoglikemia)
- Diare
- Infeksi saluran pernapasan atas
- Mual
- Batuk
- Infeksi kulit jamur
- Pembengkakan tangan atau kaki
- Muntah

Efek samping tambahan telah dilaporkan dalam penggunaan umum dengan JANUVIA, dengan sendirinya dan / atau dengan obat diabetes lainnya:

- Reaksi alergi, yang mungkin serius, termasuk ruam, gatal-gatal, dan pembengkakan wajah, bibir, lidah, dan tenggorokan yang dapat menyebabkan kesulitan bernapas atau menelan. Jika Anda memiliki reaksi alergi, berhenti mengambil JANUVIA dan segera hubungi dokter Anda. Dokter Anda mungkin meresepkan obat untuk mengobati reaksi alergi Anda dan obat yang berbeda untuk diabetes Anda.
- Radang pankreas.
- Masalah ginjal (kadang-kadang membutuhkan dialisis).
- Infeksi saluran pernapasan atas.
- Hidung tersumbat atau berair dan sakit tenggorokan.
- Konstipasi.
- Muntah.
- Sakit kepala.
- Nyeri sendi.
- Nyeri otot.
- Nyeri lengan atau kaki.

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- Sakit punggung.
- Gatal.
- Kulit melepuh.

Beritahu dokter atau apoteker jika anda mengalami efek samping yang tidak biasa, atau jika efek samping yang telah diketahui tidak membaik atau memburuk.

Bagaimana saya dapat mengetahui lebih jauh mengenai JANUVIA dan diabetes?

Anda dapat memperoleh informasi lebih lanjut melalui dokter anda atau apoteker, yang memiliki informasi lebih detail.

Berapa lama saya harus menyimpan obat saya?

Jangan gunakan obat ini setelah tanggal pada keterangan setelah kata Exp. Date pada kemasan.

Bagaimana saya harus menyimpan JANUVIA?

Simpan di bawah suhu 30℃.
Jauhkan JANUVIA dan semua obat-obatan dari jangkauan anak-anak.

HARUS DENGAN RESEP DOKTER

JANUVIA 50, Dus, 2 blister @ 14 tablet salut selaput
Reg. No.: DKL2106609817A1
JANUVIA 100, Dus, 2 blister @ 14 tablet salut selaput
Reg. No.: DKL2106609817B1

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