

Januvia® 25 mg, Film coated tablets

Each film-coated tablet contains 25 mg Sitagliptin (as monohydrate phosphate)

Januvia® 50mg, Film coated tablets

Each film-coated tablet contains 50 mg Sitagliptin (as monohydrate phosphate)

Januvia® 100mg, Film coated tablets

Each film-coated tablet contains 100 mg Sitagliptin (as monohydrate phosphate)

1 THERAPEUTIC INDICATIONS

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

Important Limitations of Use

JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

JANUVIA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUVIA. [See *Warnings and Precautions (5.1).*]

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

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

2.2 Recommendations for Use in Renal Impairment

For patients with an estimated glomerular filtration rate [eGFR] greater than or equal to 45 mL/min/1.73 m² to less than 90 mL/min/1.73 m², no dosage adjustment for JANUVIA is required.

For patients with moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 m² to less than 45 mL/min/1.73 m²), the dose of JANUVIA is 50 mg once daily.

For patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²) or with end-stage renal disease (ESRD) 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.

Because there is a need for dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of JANUVIA and periodically thereafter. There have been postmarketing reports of worsening renal function in patients with renal impairment, some of whom were prescribed inappropriate doses of sitagliptin.

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

When JANUVIA is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia. [See *Warnings and Precautions (5.4).*]

3 DOSAGE FORMS AND STRENGTHS

- 100 mg tablets are beige, round, biconvex, film-coated tablets with “277” on one side and plain on the other.

- 50 mg tablets are light beige, round, biconvex, film-coated tablets with “112” on one side and plain on the other.
- 25 mg tablets are pink, round, biconvex, film-coated tablets with “221” on one side and plain on the other.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUVIA. After initiation of JANUVIA, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUVIA should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUVIA.

5.2 Heart Failure

An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of JANUVIA prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of JANUVIA.

5.3 Acute Renal Failure

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal impairment, some of whom were prescribed inappropriate doses of sitagliptin. A return to baseline levels of renal impairment has been observed with supportive treatment and discontinuation of potentially causative agents. Consideration can be given to cautiously reinitiating JANUVIA if another etiology is deemed likely to have precipitated the acute worsening of renal function.

Assessment of renal function is recommended prior to initiating JANUVIA and periodically thereafter. A dosage adjustment is recommended in patients with moderate or severe renal impairment and in patients with ESRD requiring hemodialysis or peritoneal dialysis. [See *Dosage and Administration (2.2)*; *Use in Specific Populations (8.6)*.]

5.4 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues

When JANUVIA was used in combination with insulin or insulin secretagogues (e.g., sulfonylurea), medications known to cause hypoglycemia, the incidence of hypoglycemia was

increased over that of placebo used in combination with a sulfonylurea or with insulin. [See Adverse Reactions (6.1).] Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia. [See *Drug Interactions (7.1)*]]

5.5 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. 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 *Adverse Reactions (6.2)*.]

Angioedema has also been reported with other DPP-4 inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUVIA.

5.6 Severe and Disabling Arthralgia

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

5.7 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.

5.8 Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere in the labeling:

- Pancreatitis [see *Warnings and Precautions (5.1)*]
- Heart Failure [see *Warnings and Precautions (5.2)*]
- Acute Renal Failure [see *Warnings and Precautions (5.3)*]
- Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues [see *Warnings and Precautions (5.4)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.5)*]
- Severe and Disabling Arthralgia [see *Warnings and Precautions (5.6)*]
- Bullous Pemphigoid [see *Warnings and Precautions (5.7)*]

6.1 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, or rosiglitazone and metformin, the overall incidence of adverse reactions, hypoglycemia, 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 hypoglycemia (see Table 3); the incidence of discontinuation due to clinical adverse reactions was similar to placebo.

Two placebo-controlled monotherapy studies, one of 18- and one of 24-week duration, included patients treated with 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 $\geq 5\%$ 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. Incidences of hypoglycemia are shown in Table 3.

Table 1:
Placebo-Controlled Clinical Studies of JANUVIA Monotherapy or Add-on Combination Therapy with Pioglitazone, Metformin + Rosiglitazone, 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*

Monotherapy (18 or 24 weeks)	Number of Patients (%)	
	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 Metformin + Rosiglitazone (18 weeks)	JANUVIA 100 mg + Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone
	N = 181	N = 97
Upper Respiratory Tract Infection	10 (5.5)	5 (5.2)
Nasopharyngitis	11 (6.1)	4 (4.1)
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 insulin (with or without metformin), there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo, except for hypoglycemia (see Table 3).

In the study of JANUVIA as add-on combination therapy with metformin and rosiglitazone (Table 1), through Week 54 the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with JANUVIA and more commonly than in patients treated with placebo were: upper respiratory tract infection (JANUVIA, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%).

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

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

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

* Intent-to-treat population.

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

In a 24-week study of initial therapy with JANUVIA in combination with pioglitazone, there were no adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients and more commonly than in patients given pioglitazone alone.

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

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 acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control).

Hypoglycemia

In the above studies (N=9), 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 coadministered with a sulfonylurea or with insulin, the percentage of patients with at least one adverse reaction of hypoglycemia was higher than in the corresponding placebo group (Table 3).

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

Add-On to Glimpiride (+/- Metformin) (24 weeks)	JANUVIA 100 mg + Glimpiride (+/- Metformin)	Placebo + Glimpiride (+/- 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.

In the study of JANUVIA as add-on combination therapy with metformin and rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on JANUVIA and 0.0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on JANUVIA and 1.0% in patients given add-on placebo.

In the 24-week, placebo-controlled factorial study of initial therapy with JANUVIA in combination with metformin, the incidence of hypoglycemia was 0.6% in patients given placebo, 0.6% in patients given JANUVIA alone, 0.8% in patients given metformin alone, and 1.6% in patients given JANUVIA in combination with metformin.

In the study of JANUVIA as initial therapy with pioglitazone, one patient taking JANUVIA experienced a severe episode of hypoglycemia. There were no severe hypoglycemia episodes reported in other studies except in the study involving coadministration with insulin.

In an additional, 30-week placebo-controlled, study of patients with type 2 diabetes inadequately controlled with metformin comparing the maintenance of sitagliptin 100 mg versus withdrawal of sitagliptin when initiating basal insulin therapy, the event rate and incidence of documented symptomatic hypoglycemia (blood glucose measurement ≤ 70 mg/dL) did not differ between the sitagliptin and placebo groups.

Laboratory Tests

Across clinical studies, the incidence of laboratory adverse reactions was similar 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.

6.2 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; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis [see *Indications and Usage (1)*]; worsening renal function, including acute renal

failure (sometimes requiring dialysis); severe and disabling arthralgia; bullous pemphigoid; constipation; vomiting; headache; myalgia; pain in extremity; back pain; interstitial lung disease; pruritus; mouth ulceration; stomatitis; rhabdomyolysis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form [/https://sideeffects.health.gov.il](https://sideeffects.health.gov.il).

7 DRUG INTERACTIONS

7.1 Insulin Secretagogues or Insulin

Coadministration of JANUVIA with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia. [See *Warnings and Precautions (5.4)*.]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with JANUVIA in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*]. No adverse developmental effects were observed when sitagliptin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 30-times and 20-times, respectively, the 100 mg clinical dose, based on AUC [see *Data*].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with Hemoglobin A1c >7% and has been reported to be as high as 20-25% in women with a Hemoglobin A1c >10%.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Animal Data

In embryo-fetal development studies, sitagliptin administered to pregnant rats and rabbits during organogenesis (gestation day 6 to 20) did not adversely affect developmental outcomes at oral doses up to 250 mg/kg (30-times the 100 mg clinical dose) and 125 mg/kg (20-times the 100 mg clinical dose, respectively, based on AUC. Higher doses in rats associated with maternal toxicity increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100-times the clinical dose, based on AUC. Placental transfer of sitagliptin was observed in pregnant rats and rabbits.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 caused no functional or behavioral toxicity in offspring of rats at doses up to 1000 mg/kg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of JANUVIA in human milk, the effects on the breastfed infant, or the effects on milk production. Sitagliptin is present in rat milk and therefore possibly present in human milk [see *Data*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JANUVIA and any potential adverse effects on the breastfed infant from JANUVIA or from the underlying maternal condition.

Data

Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1.

8.4 Pediatric Use

JANUVIA is not indicated for children and adolescents under 18 years old.

8.5 Geriatric Use

Of the total number of subjects (N=3884) in pre-approval 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.

Because sitagliptin is substantially excreted by the kidney, and because aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.3)*].

8.6 Renal Impairment

Sitagliptin is excreted by the kidney, and sitagliptin exposure is increased in patients with renal impairment. Lower dosages are recommended in patients with eGFR less than 45 mL/min/1.73 m² (moderate and severe renal impairment, as well as in ESRD patients requiring dialysis). [See *Dosage and Administration (2.2)*; *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

In the event of an overdose, it is reasonable to employ 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.

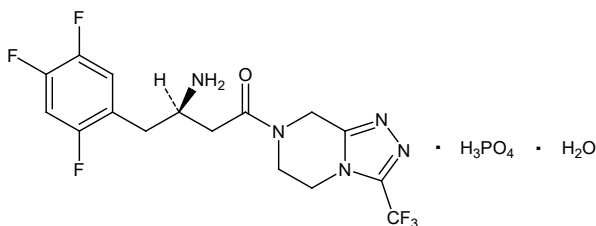
Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

11 DESCRIPTION

JANUVIA Tablets contain sitagliptin phosphate, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

Sitagliptin phosphate monohydrate is described chemically as 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 empirical formula is C₁₆H₁₅F₆N₅O•H₃PO₄•H₂O 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. Each film-coated tablet of JANUVIA contains 32.13, 64.25, or 128.5 mg of sitagliptin phosphate monohydrate, which is equivalent to 25, 50, or 100 mg, respectively, of free base and the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, sodium stearyl fumarate, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide yellow, and iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes mellitus by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity *in vitro* at concentrations approximating those from therapeutic doses.

12.2 Pharmacodynamics

General

In patients with type 2 diabetes mellitus, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition

resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

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

Sitagliptin and Metformin hydrochloride Coadministration

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear how these findings relate to changes in glycemic control in patients with type 2 diabetes mellitus.

Cardiac Electrophysiology

In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline was observed at 3 hours 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 times higher than the peak concentrations following a 100 mg dose.

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

12.3 Pharmacokinetics

The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes mellitus. Following a single oral 100 mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 $\mu\text{M}\cdot\text{hr}$, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin increased in a dose-proportional manner and 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 mellitus.

Absorption

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. The absolute bioavailability of sitagliptin is approximately 87%.

Effect of Food

Coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.

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%).

Elimination

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

Metabolism

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.

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 (P-gp), which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a P-gp inhibitor, did not reduce the renal clearance of sitagliptin.

Specific Populations

Patients with Renal Impairment

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to less than 45 mL/min/1.73 m², and an approximately 4-fold increase was observed in patients with severe renal impairment, including patients with ESRD on hemodialysis, as compared to normal healthy control subjects.

Patients with Hepatic Impairment

In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100 mg dose of sitagliptin. These differences are not considered to be clinically meaningful.

There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score >9).

Effects of Age, Body Mass Index (BMI), Gender, and Race

Based on a population pharmacokinetic analysis or a composite analysis of available pharmacokinetic data, BMI, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. 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.

Drug Interaction Studies

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-gp substrate, but does not inhibit P-gp 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, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, digoxin, warfarin, or an oral contraceptive (ethinyl estradiol and norethindrone) (Table 4), providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, P-gp, and organic cationic transporter (OCT).

**Table 4:
Effect of Sitagliptin on Systemic Exposure of Coadministered Drugs**

Coadministered Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without sitagliptin) No Effect = 1.00		
				AUC [†]	C _{max}
Digoxin	0.25 mg [‡] once daily for 10 days	100 mg [‡] once daily for 10 days	Digoxin	1.11 [§]	1.18
Glyburide	1.25 mg	200 mg [‡] once daily for 6 days	Glyburide	1.09	1.01
Simvastatin	20 mg	200 mg [‡] once daily for 5 days	Simvastatin	0.85 [¶]	0.80
			Simvastatin Acid	1.12 [¶]	1.06
Rosiglitazone	4 mg	200 mg [‡] once daily for 5 days	Rosiglitazone	0.98	0.99
Warfarin	30 mg single dose on day 5	200 mg [‡] once daily for 11 days	S(-) Warfarin	0.95	0.89
			R(+) Warfarin	0.99	0.89
Ethinyl estradiol and norethindrone	21 days once daily of 35 µg ethinyl estradiol with norethindrone 0.5 mg x 7 days, 0.75 mg x 7 days, 1.0 mg x 7 days	200 mg [‡] once daily for 21 days	Ethinyl estradiol	0.99	0.97
			Norethindrone	1.03	0.98
Metformin HCl	1000 mg [‡] twice daily for 14 days	50 mg [‡] twice daily for 7 days	Metformin	1.02 [#]	0.97

* All doses administered as single dose unless otherwise specified

† AUC is reported as AUC_{0-∞} unless otherwise specified

‡ Multiple dose

§ AUC_{0-24hr}

¶ AUC_{0-last}

AUC_{0-12hr}

Effects of Other Drugs on Sitagliptin

Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by coadministered medications (Table 5).

**Table 5:
Effect of Coadministered Drugs on Systemic Exposure of Sitagliptin**

Coadministered Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC [†]	C _{max}
Cyclosporine	600 mg once daily	100 mg once daily	Sitagliptin	1.29	1.68

Metformin HCl	1000 mg [‡] twice daily for 14 days	50 mg [‡] twice daily for 7 days	Sitagliptin	1.02 [§]	1.05
---------------	---	--	-------------	-------------------	------

* All doses administered as single dose unless otherwise specified

† AUC is reported as AUC_{0-∞} unless otherwise specified

‡ Multiple dose

§ AUC_{0-12hr}

13 NONCLINICAL TOXICOLOGY

13.1 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).

14 CLINICAL STUDIES

There were approximately 5200 patients with type 2 diabetes randomized in nine double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of sitagliptin on glycemic control. In a pooled analysis of seven of these studies, the ethnic/racial distribution was approximately 59% white, 20% Hispanic, 10% Asian, 6% black, and 6% other groups. Patients had an overall mean age of approximately 55 years (range 18 to 87 years). In addition, an active (glipizide)-controlled study of 52-weeks duration was conducted in 1172 patients with type 2 diabetes who had inadequate glycemic control on metformin.

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

14.1 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 washout period of about 7 weeks. Patients with inadequate glycemic control (A1C 7% to 10%)

after the washout period were randomized after completing a 2-week single-blind placebo run-in period; patients not currently on antihyperglycemic agents (off therapy for at least 8 weeks) with inadequate glycemic control (A1C 7% to 10%) were randomized after completing the 2-week single-blind placebo run-in period. In the 18-week study, 521 patients were randomized to placebo, 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 A1C, FPG, and 2-hour PPG compared to placebo (Table 6). 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 A1C compared to placebo was not affected by gender, age, race, prior antihyperglycemic therapy, or baseline BMI. As is typical for trials of agents to treat type 2 diabetes, the mean reduction in A1C with JANUVIA appears to be related to the degree of A1C elevation at baseline. In these 18- and 24-week studies, among patients who were not on an antihyperglycemic agent at study entry, the reductions from baseline in A1C were -0.7% and -0.8%, respectively, for those given JANUVIA, and -0.1% and -0.2%, respectively, for those given placebo. Overall, the 200 mg daily dose did not provide greater glycemic efficacy than the 100 mg daily dose. The effect of 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 6:
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 N = 193	Placebo N = 103	JANUVIA 100 mg N = 229	Placebo N = 244
A1C (%)				
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* (12.3).]

14.2 Combination Therapy

Add-on Combination Therapy with Metformin

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with metformin. Patients already on metformin HCl (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 HCl (at a dose of at least 1500 mg per day) in monotherapy. Patients with inadequate glycemic control (A1C 7% to 10%) were randomized to the addition of either 100 mg of 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 A1C, FPG, and 2-hour PPG compared to placebo with metformin (Table 7). 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 7:
Glycemic Parameters at Final Visit (24-Week Study)
for JANUVIA in Add-on Combination Therapy 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.

Initial Combination Therapy with Metformin

A total of 1091 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind, placebo-controlled factorial study designed to assess the efficacy of sitagliptin as initial therapy in combination with metformin. Patients on an antihyperglycemic agent (N=541) discontinued the agent, and underwent a diet, exercise, and drug washout period of up to 12 weeks duration. After the washout period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized after completing a 2-week single-blind placebo run-in period. Patients not on antihyperglycemic agents at study entry (N=550) with inadequate glycemic control (A1C 7.5% to 11%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. Approximately equal numbers of patients were randomized to receive initial therapy with placebo, 100 mg of JANUVIA once daily, 500 mg or 1000 mg of metformin HCl twice daily, or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin HCl twice daily. Patients who failed to meet specific glycemic goals during the study were treated with glyburide (glibenclamide) rescue.

Initial therapy with the combination of JANUVIA and metformin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to JANUVIA alone (Table 8, Figure 1). Mean reductions from baseline in A1C were generally greater for patients with higher baseline A1C values. For patients not on an antihyperglycemic agent at study entry, mean reductions from baseline in A1C were: JANUVIA 100 mg once daily, -1.1%; metformin HCl 500 mg bid, -1.1%; metformin HCl 1000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin HCl 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin HCl 1000 mg bid, -1.9%; and for patients receiving placebo, -0.2%. Lipid effects were generally neutral. The decrease in body weight in the groups given sitagliptin in combination with metformin was similar to that in the groups given metformin alone or placebo.

**Table 8:
Glycemic Parameters at Final Visit (24-Week Study)
for Sitagliptin and Metformin, Alone and in Combination as Initial Therapy***

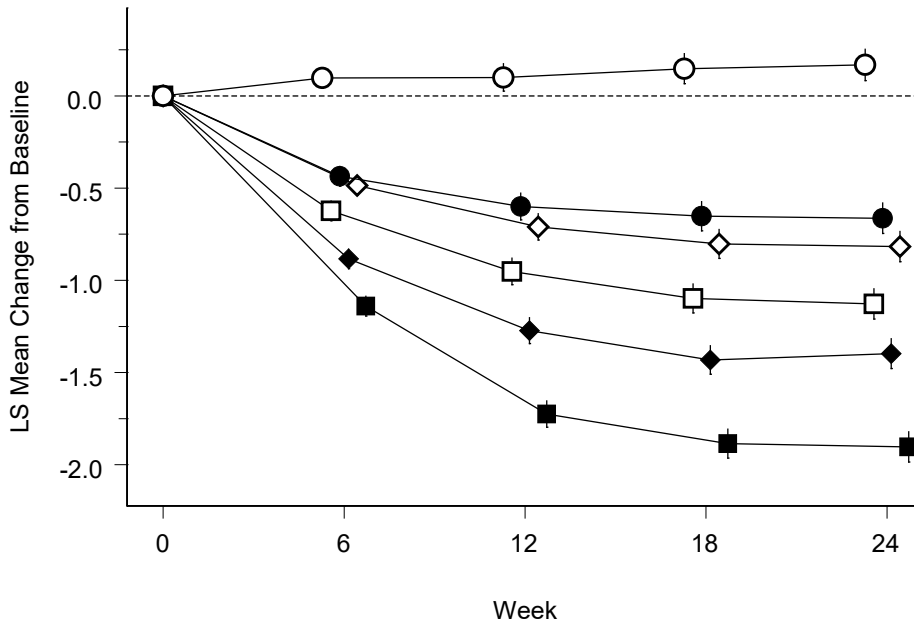
	Placebo	Sitagliptin (JANUVIA) 100 mg QD	Metformin HCl 500 mg bid	Metformin HCl 1000 mg bid	Sitagliptin 50 mg bid + Metformin HCl 500 mg bid	Sitagliptin 50 mg bid + Metformin HCl 1000 mg bid
A1C (%)	N = 165	N = 175	N = 178	N = 177	N = 183	N = 178
Baseline (mean)	8.7	8.9	8.9	8.7	8.8	8.8
Change from baseline (adjusted mean [†])	0.2	-0.7	-0.8	-1.1	-1.4	-1.9
Difference from placebo (adjusted mean [†]) (95% CI)		-0.8 [‡] (-1.1, -0.6)	-1.0 [‡] (-1.2, -0.8)	-1.3 [‡] (-1.5, -1.1)	-1.6 [‡] (-1.8, -1.3)	-2.1 [‡] (-2.3, -1.8)
Patients (%) achieving A1C <7%	15 (9%)	35 (20%)	41 (23%)	68 (38%)	79 (43%)	118 (66%)
% Patients receiving rescue medication	32	21	17	12	8	2
FPG (mg/dL)	N = 169	N = 178	N = 179	N = 179	N = 183	N = 180
Baseline (mean)	196	201	205	197	204	197
Change from baseline (adjusted mean [†])	6	-17	-27	-29	-47	-64
Difference from placebo (adjusted mean [†]) (95% CI)		-23 [‡] (-33, -14)	-33 [‡] (-43, -24)	-35 [‡] (-45, -26)	-53 [‡] (-62, -43)	-70 [‡] (-79, -60)
2-hour PPG (mg/dL)	N = 129	N = 136	N = 141	N = 138	N = 147	N = 152
Baseline (mean)	277	285	293	283	292	287
Change from baseline (adjusted mean [†])	0	-52	-53	-78	-93	-117
Difference from placebo (adjusted mean [†]) (95% CI)		-52 [‡] (-67, -37)	-54 [‡] (-69, -39)	-78 [‡] (-93, -63)	-93 [‡] (-107, -78)	-117 [‡] (-131, -102)

* Intent-to-treat population using last observation on study prior to glyburide (glibenclamide) rescue therapy.

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

‡ p<0.001 compared to placebo.

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



- 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.

*All Patients Treated Population: least squares means adjusted for prior antihyperglycemic therapy and baseline value.

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

Active-Controlled Study vs Glipizide in Combination with Metformin

The efficacy of JANUVIA was evaluated in a 52-week, double-blind, glipizide-controlled noninferiority trial in patients with type 2 diabetes. Patients not on treatment or on other antihyperglycemic agents entered a run-in treatment period of up to 12 weeks duration with metformin HCl monotherapy (dose of ≥ 1500 mg per day) which included washout of medications other than metformin, if applicable. After the run-in period, those with inadequate glycemic control (A1C 6.5% to 10%) were randomized 1:1 to the addition of JANUVIA 100 mg once daily or glipizide for 52 weeks. Patients receiving glipizide were given an initial dosage of 5 mg/day and then electively titrated over the next 18 weeks to a maximum dosage of 20 mg/day as needed to optimize glycemic control. Thereafter, the glipizide dose was to be kept constant, except for down-titration to prevent hypoglycemia. The mean dose of glipizide after the titration period was 10 mg.

After 52 weeks, JANUVIA and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis (Table 9). These results were consistent with the per protocol analysis (Figure 2). A conclusion in favor of the non-inferiority of JANUVIA to glipizide may be limited to patients with baseline A1C comparable to those included in the study (over 70% of patients had baseline A1C <8% and over 90% had A1C <9%).

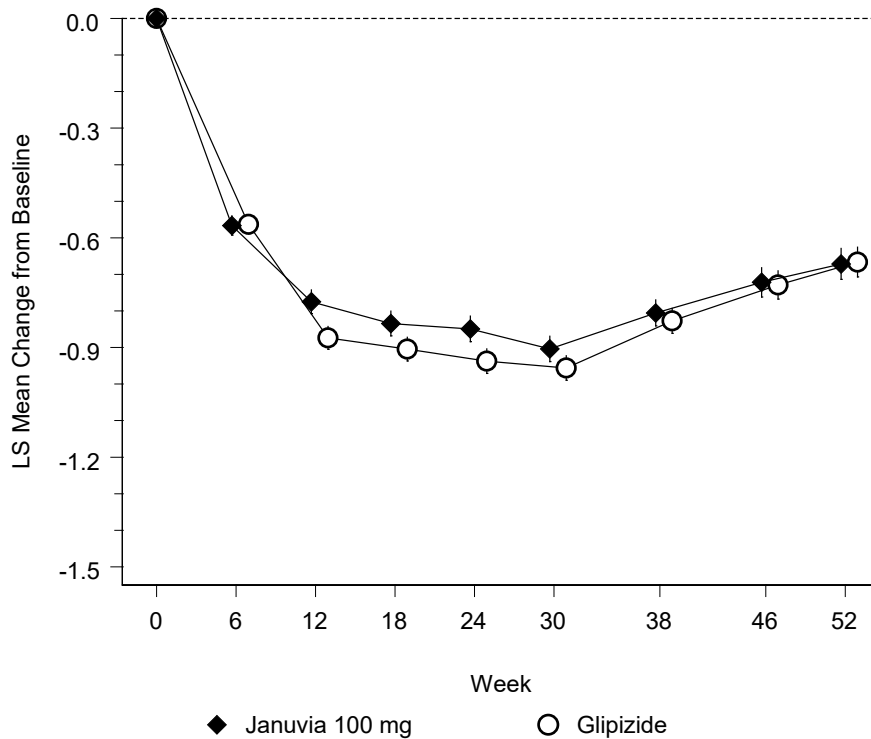
Table 9:
Glycemic Parameters in a 52-Week Study Comparing
JANUVIA to Glipizide as Add-On Therapy in Patients Inadequately
Controlled on Metformin
(Intent-to-Treat Population)*

	JANUVIA 100 mg	Glipizide
A1C (%)	N = 576	N = 559
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean [†])	-0.5	-0.6
FBG (mg/dL)	N = 583	N = 568
Baseline (mean)	166	164
Change from baseline (adjusted mean [†])	-8	-8

* The intent-to-treat analysis used the patients' last observation in the study prior to discontinuation.

[†] Least squares means adjusted for prior antihyperglycemic therapy status and baseline A1C value.

Figure 2: Mean Change from Baseline for A1C (%) Over 52 Weeks in a Study
Comparing JANUVIA to Glipizide as Add-On Therapy in
Patients Inadequately Controlled on Metformin
(Per Protocol Population)*



* The per protocol population (mean baseline A1C of 7.5%) included patients without major protocol violations who had observations at baseline and at Week 52.

The incidence of hypoglycemia in the JANUVIA group (4.9%) was significantly ($p < 0.001$) lower than that in the glipizide group (32.0%). Patients treated with JANUVIA exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs +1.1 kg).

Add-on Combination Therapy with Pioglitazone

A total of 353 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with pioglitazone. Patients on any oral antihyperglycemic agent in monotherapy (N=212) or on a PPAR γ agent in combination therapy (N=106) or not on an antihyperglycemic agent (off therapy for at least 8 weeks, N=34) were switched to monotherapy with pioglitazone (at a dose of 30-45 mg per day), and completed a run-in period of approximately 12 weeks in duration. After the run-in period on pioglitazone monotherapy, patients with inadequate glycemic control (A1C 7% to 10%) were randomized to the addition of either 100 mg of 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 were A1C and fasting glucose. In combination with pioglitazone, JANUVIA provided significant improvements in A1C and FPG compared to placebo with pioglitazone (Table 10). 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 10:
Glycemic Parameters at Final Visit (24-Week Study)
for JANUVIA in Add-on Combination Therapy 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.

Initial Combination Therapy with Pioglitazone

A total of 520 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind study designed to assess the efficacy of JANUVIA as initial therapy in combination with pioglitazone. Patients not on antihyperglycemic agents at study entry (<4 weeks cumulative therapy over the past 2 years, and with no treatment over the prior 4 months) with inadequate glycemic control (A1C 8% to 12%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. Approximately equal numbers of patients were randomized to receive initial therapy with 100 mg of JANUVIA in combination with 30 mg of pioglitazone once daily or 30 mg of pioglitazone once daily as monotherapy. There was no glycemic rescue therapy in this study.

Initial therapy with the combination of JANUVIA and pioglitazone provided significant improvements in A1C, FPG, and 2-hour PPG compared to pioglitazone monotherapy (Table

11). The improvement in A1C was generally consistent across subgroups defined by gender, age, race, baseline BMI, baseline A1C, or duration of disease. In this study, patients treated with JANUVIA in combination with pioglitazone had a mean increase in body weight of 1.1 kg compared to pioglitazone alone (3.0 kg vs. 1.9 kg). Lipid effects were generally neutral.

Table 11:
Glycemic Parameters at Final Visit (24-Week Study)
for JANUVIA in Combination with Pioglitazone as Initial Therapy*

	JANUVIA 100 mg + Pioglitazone	Pioglitazone
A1C (%)	N = 251	N = 246
Baseline (mean)	9.5	9.4
Change from baseline (adjusted mean [†])	-2.4	-1.5
Difference from pioglitazone (adjusted mean [†]) (95% CI)	-0.9 [‡] (-1.1, -0.7)	
Patients (%) achieving A1C <7%	151 (60%)	68 (28%)
FPG (mg/dL)	N = 256	N = 253
Baseline (mean)	203	201
Change from baseline (adjusted mean [†])	-63	-40
Difference from pioglitazone (adjusted mean [†]) (95% CI)	-23 [‡] (-30, -15)	
2-hour PPG (mg/dL)	N = 216	N = 211
Baseline (mean)	283	284
Change from baseline (adjusted mean [†])	-114	-69
Difference from pioglitazone (adjusted mean [†]) (95% CI)	-45 [‡] (-57, -32)	

* Intent-to-treat population using last observation on study.

[†] Least squares means adjusted for baseline value.

[‡] p<0.001 compared to placebo + pioglitazone.

Add-on Combination Therapy with Metformin and Rosiglitazone

A total of 278 patients with type 2 diabetes participated in a 54-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with metformin and rosiglitazone. Patients on dual therapy with metformin HCl ≥1500 mg/day and rosiglitazone ≥4 mg/day or with metformin HCl ≥1500 mg/day and pioglitazone ≥30 mg/day (switched to rosiglitazone ≥4 mg/day) entered a dose-stable run-in period of 6 weeks. Patients on other dual therapy were switched to metformin HCl ≥1500 mg/day and rosiglitazone ≥4 mg/day in a dose titration/stabilization run-in period of up to 20 weeks in duration. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized 2:1 to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the study were treated with glipizide (or other sulfonylurea) rescue. The primary time point for evaluation of glycemic parameters was Week 18.

In combination with metformin and rosiglitazone, JANUVIA provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin and rosiglitazone (Table 12) at Week 18. At Week 54, mean reduction in A1C was -1.0% for patients treated with JANUVIA and -0.3% for patients treated with placebo in an analysis based on the intent-to-treat population. Rescue therapy was used in 18% of patients treated with JANUVIA 100 mg and 40% of patients treated with placebo. There was no significant difference between JANUVIA and placebo in body weight change.

Table 12:
Glycemic Parameters at Week 18
for JANUVIA in Add-on Combination Therapy with Metformin and Rosiglitazone*

	JANUVIA 100 mg + Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone
A1C (%)	N = 176	N = 93
Baseline (mean)	8.8	8.7
Change from baseline (adjusted mean [†])	-1.0	-0.4
Difference from placebo + rosiglitazone + metformin (adjusted mean [†]) (95% CI)	-0.7 [‡] (-0.9, -0.4)	
Patients (%) achieving A1C <7%	39 (22%)	9 (10%)
FPG (mg/dL)	N = 179	N = 94
Baseline (mean)	181	182
Change from baseline (adjusted mean [†])	-30	-11
Difference from placebo + rosiglitazone + metformin (adjusted mean [†]) (95% CI)	-18 [‡] (-26, -10)	
2-hour PPG (mg/dL)	N = 152	N = 80
Baseline (mean)	256	248
Change from baseline (adjusted mean [†])	-59	-21
Difference from placebo + rosiglitazone + metformin (adjusted mean [†]) (95% CI)	-39 [‡] (-51, -26)	

* Intent-to-treat population using last observation on study prior to glipizide (or other sulfonylurea) rescue therapy.

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

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

Add-on Combination Therapy with Glimepiride, with or without Metformin

A total of 441 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with glimepiride, with or without metformin. Patients entered a run-in treatment period on glimepiride (≥4 mg per day) alone or glimepiride in combination with metformin HCl (≥1500 mg per day). After a dose-titration and dose-stable run-in period of up to 16 weeks and a 2-week placebo run-in period, patients with inadequate glycemic control (A1C 7.5% to 10.5%) were randomized to the addition of either 100 mg of 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 glimepiride, with or without metformin, JANUVIA provided significant improvements in A1C and FPG compared to placebo (Table 13). In the entire study population (patients on JANUVIA in combination with glimepiride and patients on JANUVIA in combination with glimepiride and metformin), a mean reduction from baseline relative to placebo in A1C of -0.7% and in FPG of -20 mg/dL was seen. Rescue therapy was used in 12% of patients treated with JANUVIA 100 mg and 27% of patients treated with placebo. In this study, patients treated with JANUVIA had a mean increase in body weight of 1.1 kg vs. placebo (+0.8 kg vs. -0.4 kg). In addition, there was an increased rate of hypoglycemia. [See *Warnings and Precautions (5.4); Adverse Reactions (6.1).*]

Table 13:
Glycemic Parameters at Final Visit (24-Week Study)
for JANUVIA as Add-On Combination Therapy with Glimepiride, with or without Metformin*

	JANUVIA 100 mg + Glimepiride	Placebo + Glimepiride	JANUVIA 100 mg + Glimepiride + Metformin	Placebo + Glimepiride + Metformin
A1C (%)	N = 102	N = 103	N = 115	N = 105
Baseline (mean)	8.4	8.5	8.3	8.3
Change from baseline (adjusted mean [†])	-0.3	0.3	-0.6	0.3
Difference from placebo (adjusted mean [†]) (95% CI)	-0.6 [‡] (-0.8, -0.3)		-0.9 [‡] (-1.1, -0.7)	
Patients (%) achieving A1C <7%	11 (11%)	9 (9%)	26 (23%)	1 (1%)
FPG (mg/dL)	N = 104	N = 104	N = 115	N = 109
Baseline (mean)	183	185	179	179
Change from baseline (adjusted mean [†])	-1	18	-8	13
Difference from placebo (adjusted mean [†]) (95% CI)	-19 [§] (-32, -7)		-21 [‡] (-32, -10)	

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

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

‡ p<0.001 compared to placebo.

§ p<0.01 compared to placebo.

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

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA as add-on to insulin therapy (with or without metformin). The racial distribution in this study was approximately 70% white, 18% Asian, 7% black, and 5% other groups. Approximately 14% of the patients in this study were Hispanic. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin HCl (≥ 1500 mg per day). Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a pre-mixed insulin. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized to the addition of either 100 mg of 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 A1C, FPG, and 2-hour PPG compared to placebo (Table 14). 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 (5.4); Adverse Reactions (6.1).]

Table 14:
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.

Maintenance of JANUVIA During Initiation and Titration of Insulin Glargine

A total of 746 patients with type 2 diabetes (mean baseline HbA1C 8.8%, disease duration 10.8 years) participated in a 30-week, randomized, double-blind, placebo-controlled study to assess the

efficacy and safety of continuing JANUVIA during the initiation and uptitration of insulin glargine. Patients who were on a stable dose of metformin HCl (≥ 1500 mg/day) in combination with a DPP-4 inhibitor and/or sulfonylurea but with inadequate glycemic control (A1C 7.5% to 11%) were enrolled in the study. Those on metformin and JANUVIA (100 mg/day) directly entered the double-blind treatment period; those on another DPP-4 inhibitor and/or on a sulfonylurea entered a 4-8 week run-in period in which they were maintained on metformin and switched to JANUVIA (100 mg); other DPP-4 inhibitors and sulfonylureas were discontinued. At randomization patients were randomized either to continue JANUVIA or to discontinue JANUVIA and switch to a matching placebo. On the day of randomization, insulin glargine was initiated at a dose of 10 units subcutaneously in the evening. Patients were instructed to uptitrate their insulin dose in the evening based on fasting blood glucose measurements to achieve a target of 72- 100 mg/dL.

At 30 weeks, the mean reduction in A1C was greater in the sitagliptin group than in the placebo group (Table 15). At the end of the trial, 27.3% of patients in the sitagliptin group and 27.3% in the placebo group had a fasting plasma glucose (FPG) in the target range; there was no significant difference in insulin dose between arms.

Table 15:
Change from Baseline in A1C and FPG at Week 30 in the Maintenance of JANUVIA During Initiation and Titration of Insulin Glargine Study

	Sitagliptin 100 mg + Metformin + Insulin Glargine	Placebo + Metformin + Insulin Glargine
A1C (%)	N = 373[†]	N = 370[†]
Baseline (mean)	8.8	8.8
Week 30 (mean)	6.9	7.3
Change from baseline (adjusted mean) [*]	-1.9	-1.4
Difference from placebo (adjusted mean) (95% CI) [*]	-0.4 (-0.6, -0.3) [‡]	
Patients (%) with A1C <7%	202 (54.2%)	131 (35.4%)
FPG (mg/dL)	N = 373[†]	N = 370[†]
Baseline (mean)	199	201
Week 30 (mean)	118	123
Change from baseline (adjusted mean) [*]	-81	-76

^{*} Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputation to model washout of the treatment effect using placebo data for all subjects having missing Week 30 data.

[†] N is the number of randomized and treated patients.

[‡] p<0.001 compared to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets JANUVIA, 25 mg, are pink, round, biconvex, film-coated tablets with “221” on one side and plain on the other.

They are supplied as follows: pack sizes of 7, 10, 14, 28, 30 tablets. Not all pack sizes may be marketed.

Tablets JANUVIA, 50 mg, are light beige, round, biconvex, film-coated tablets with “112” on one side and plain on the other.

They are supplied as follows: pack sizes of 7, 10, 14, 28, 30 tablets. Not all pack sizes may be marketed.

Tablets JANUVIA, 100 mg, are beige, round, biconvex, film-coated tablets with “277” on one side and plain on the other.

They are supplied as follows: pack sizes of 7, 10, 14, 28, 30 tablets. Not all pack sizes may be marketed.

Storage

Store below 30°C.

Manufacturer:

Merck Sharp & Dohme Corp., NJ, USA.

License holder:

Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O. Box 7121, Petah-Tikva, 49170.

Drug registration no. listed in the official registry of the Ministry of Health:

Januvia 25mg : 138.13.31554

Januvia 50mg : 138.14.31555

Januvia 100mg :138.15.31556

Revised on April 2021 according to MOHs guidelines.