

PRODUCT MONOGRAPH

 **JANUVIA™**

sitagliptin tablets
(as sitagliptin phosphate monohydrate)

100 mg

Oral Antihyperglycemic Agent
DPP-4 inhibitor
Incretin Enhancer

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JANUVIA™

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
oral	tablet 100 mg	<i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

JANUVIA™ (sitagliptin) is indicated in combination with metformin in adult patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise, plus metformin do not provide adequate glycemic control.

Geriatrics (≥65 years of age): No dosage adjustment is required base on age however, greater sensitivity of some older individuals cannot be ruled out (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (<18 years of age): Safety and effectiveness of JANUVIA™ in pediatric patients have not been established. Therefore, JANUVIA™ should not be used in this population.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation (see WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions and ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions). For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

General

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

Hypersensitivity Reactions

There have been post-marketing 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 CONTRAINDICATIONS and ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions).

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women; therefore, the safety of JANUVIA™ in pregnant women is not known. JANUVIA™ is not recommended for use in pregnancy (see also TOXICOLOGY).

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

Pediatrics (<18 years of age): Safety and effectiveness of JANUVIA™ in pediatric patients have not been established. Therefore, JANUVIA™ should not be used in this population.

Geriatrics (≥65 years of age): In clinical studies, 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 geriatric and younger patients, greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney. Renal function should be assessed prior to initiating dosing and periodically thereafter in geriatric patients because they are more likely to have decreased renal function (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Cardiovascular - Patients with Congestive Heart Failure: A limited number of patients with congestive heart failure participated in clinical studies of sitagliptin. In studies of sitagliptin in combination with metformin, patients with congestive heart failure requiring pharmacological therapy or NYHA Class III or IV congestive heart failure were excluded. Patients with Classes I and II were included in small number. Use in this population is not recommended.

Hepatic Insufficiency: There are limited clinical experiences in patients with moderate hepatic insufficiency and no clinical experience in patients with severe hepatic insufficiency. Use in patients with severe hepatic insufficiency is not recommended (see ACTION AND CLINICAL PHARMACOLOGY).

Renal Insufficiency: Clinical study experience with JANUVIA™ in patients with moderate or severe renal insufficiency including those with ESRD is limited. Use in these patients is not recommended (see ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests

Response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA_{1c} levels, with a goal of decreasing these levels towards the normal range. HbA_{1c} is especially useful for evaluating long-term glycemic control.¹ Sitagliptin is substantially excreted by the kidney. Renal function should be assessed prior to initiating dosing and periodically thereafter.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

JANUVIA™ was generally well tolerated in controlled clinical studies as a combination therapy with metformin, with the overall incidence of side effects similar to that reported with placebo.

The incidences of serious adverse experiences and discontinuation of therapy due to clinical adverse experiences were also similar to placebo. The most frequent adverse reaction in trials of JANUVIA™ as add-on combination therapy with metformin (reported regardless of causality, and more common with JANUVIA™ than other treatments) was nasopharyngitis.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In a 24-week placebo-controlled clinical study of patients receiving sitagliptin (100 mg daily) as add-on combination therapy with metformin, the incidence of adverse reactions, reported regardless of causality assessment, in ≥1% of patients are shown in Table 1.

Table 1 - Adverse reactions $\geq 1\%$ in any treatment group (regardless of causality) reported in patients in a 24-week placebo-controlled, double-blind clinical trial of JANUVIA™ in add-on combination use with metformin

Body system/Organ class Adverse event	Number of patients (%)	
	Sitagliptin 100 mg + Metformin n=464	Placebo + Metformin n=237
Ear and labyrinth disorders		
Vertigo	5 (1.1)	4 (1.7)
Eye disorders		
Vision blurred	1 (0.2)	3 (1.3)
Gastrointestinal disorders		
Abdominal pain	2 (0.4)	6 (2.5)
Abdominal pain upper	6 (1.3)	2 (0.8)
Constipation	5 (1.1)	1 (0.4)
Diarrhea	11 (2.4)	6 (2.5)
Nausea	6 (1.3)	2 (0.8)
Vomiting	5 (1.1)	2 (0.8)
General disorders and administration site conditions		
Fatigue	2 (0.4)	4 (1.7)
Edema peripheral	4 (0.9)	3 (1.3)
Infections and infestations		
Bronchitis	12 (2.6)	6 (2.5)
Bronchitis acute	2 (0.4)	3 (1.3)
Gastroenteritis	4 (0.9)	5 (2.1)
Influenza	19 (4.1)	12 (5.1)
Nasopharyngitis	19 (4.1)	7 (3.0)
Pharyngitis	6 (1.3)	1 (0.4)
Pneumonia	5 (1.1)	0 (0.0)
Sinusitis	7 (1.5)	2 (0.8)
Tooth infection	5 (1.1)	2 (0.8)
Upper respiratory tract infection	34 (7.3)	22 (9.3)
Urinary tract infection	9 (1.9)	2 (0.8)
Injury, poisoning and procedural complications		
Contusion	5 (1.1)	1 (0.4)
Investigations		
Blood glucose increased	3 (0.6)	6 (2.5)
Metabolism and nutrition disorders		
Hyperglycemia	2 (0.4)	7 (3.0)
Hypoglycemia	6 (1.3)	5 (2.1)
Musculoskeletal and connective tissue disorders		
Arthralgia	14 (3.0)	1 (0.4)
Back pain	15 (3.2)	6 (2.5)
Muscle spasm	1 (0.2)	3 (1.3)

Myalgia	1 (0.2)	3 (1.3)
Pain in extremity	5 (1.1)	4 (1.7)
Shoulder pain	3 (0.6)	3 (1.3)
Nervous system disorders		
Dizziness	7 (1.5)	2 (0.8)
Headache	12 (2.6)	7 (3.0)
Sciatica	1 (0.2)	3 (1.3)
Sinus headache	0 (0.0)	3 (1.3)
Psychiatric disorders		
Insomnia	5 (1.1)	3 (1.3)
Renal and urinary disorders		
Nephrolithiasis	3 (0.6)	3 (1.3)
Respiratory, thoracic and mediastinal disorders		
Cough	14 (3.0)	4 (1.7)
Vascular disorders		
Hypertension	7 (1.5)	6 (2.5)

In a pre-specified analysis, the incidence of hypoglycemia in patients treated with sitagliptin plus metformin (1.3%) was similar to patients treated with placebo and metformin (2.1%). The incidence of selected gastrointestinal adverse experiences in patients treated with sitagliptin and metformin was also similar to placebo and metformin.

In pooled studies of up to one year duration which compared sitagliptin added to metformin or a sulfonylurea agent (glipizide) added to metformin, adverse reactions, reported regardless of causality assessment, in $\geq 1\%$ of patients are shown in Table 2.

Table 2 - Adverse reactions $\geq 1\%$ in any treatment group (regardless of causality) reported in patients from double-blind clinical trials of JANUVIA™ in add-on combination use with metformin in studies up to one year compared to a sulfonylurea agent (glipizide)

Body system/Organ class Adverse event	Number of patients (%)	
	Sitagliptin 100 mg + Metformin n=979	Glipizide + Metformin n=748
Gastrointestinal disorders		
Abdominal pain	10 (1.0)	6 (0.8)
Abdominal pain upper	13 (1.3)	7 (0.9)
Constipation	17 (1.7)	13 (1.7)
Diarrhea	42 (4.3)	36 (4.8)
Dyspepsia	14 (1.4)	12 (1.6)
Nausea	19 (1.9)	16 (2.1)
Toothache	2 (0.2)	13 (1.7)
Vomiting	11 (1.1)	9 (1.2)
General disorders and administration site conditions		
Fatigue	20 (2.0)	8 (1.1)
Non-cardiac chest pain	10 (1.0)	6 (0.8)
Edema peripheral	16 (1.6)	14 (1.9)
Infections and infestations		

Bronchitis	27 (2.8)	22 (2.9)
Cellulitis	7 (0.7)	10 (1.3)
Gastroenteritis	19 (1.9)	13 (1.7)
Gastroenteritis viral	8 (0.8)	9 (1.2)
Herpes zoster	4 (0.4)	8 (1.1)
Influenza	35 (3.6)	32 (4.3)
Nasopharyngitis	75 (7.7)	49 (6.6)
Sinusitis	20 (2.0)	12 (1.6)
Upper respiratory tract infection	78 (8.0)	70 (9.4)
Urinary tract infection	41 (4.2)	21 (2.8)
Investigations		
Blood glucose decreased	5 (0.5)	16 (2.1)
Blood glucose increased	13 (1.3)	5 (0.7)
Weight increased	1 (0.1)	8 (1.1)
Metabolism and nutrition disorders		
Hyperglycemia	10 (1.0)	6 (0.8)
Hypoglycemia	32 (3.3)	217 (29.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	34 (3.5)	29 (3.9)
Back pain	39 (4.0)	32 (4.3)
Muscle spasms	9 (0.9)	8 (1.1)
Neck pain	4 (0.4)	8 (1.1)
Osteoarthritis	18 (1.8)	5 (0.7)
Pain in extremity	23 (2.3)	9 (1.2)
Shoulder pain	7 (0.7)	14 (1.9)
Nervous system disorders		
Dizziness	26 (2.7)	14 (1.9)
Headache	34 (3.5)	31 (4.1)
Hypoaesthesia	3 (0.3)	11 (1.5)
Psychiatric disorders		
Anxiety	13 (1.3)	7 (0.9)
Depression	10 (1.0)	7 (0.9)
Insomnia	12 (1.2)	11 (1.5)
Reproductive system and breast disorders		
Erectile dysfunction	6 (0.6)	8 (1.1)
Respiratory, thoracic and mediastinal disorders		
Cough	19 (1.9)	23 (3.1)
Pharyngolaryngeal pain	10 (1.0)	9 (1.2)
Sinus congestion	5 (0.5)	8 (1.1)
Eczema	4 (0.4)	12 (1.6)
Vascular disorders		
Hypertension	33 (3.4)	29 (3.9)

Less Common Clinical Trial Adverse Drug Reactions ≥0.1% and <1% (Drug-Related and Greater than Placebo)

Cardiac Disorders: bundle branch block

Gastrointestinal Disorders: abdominal discomfort, abdominal pain upper, diarrhea, dyspepsia, flatulence, reflux esophagitis disease, retching

General Disorders and Administration Site Conditions: face edema, malaise, peripheral edema, pain

Hepatobiliary Disorders: hepatic steatosis

Infections and Infestations: gastric ulcer helicobacter, helicobacter gastritis, upper respiratory tract infection

Investigations: blood glucose decreased

Metabolism and Nutrition Disorders: decreased appetite, hypoglycemia

Musculoskeletal and Connective Tissue Disorders: muscle tightness

Nervous System Disorders: migraine, neuropathy peripheral, parosmia, somnolence

Reproductive System and Breast Disorders: dysmenorrhea, erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: cough

Skin and Subcutaneous Tissue Disorders: exanthem, rash, urticaria

Vascular Disorders: orthostatic hypotension

Nausea was the only drug-related adverse reaction reported by the investigator that occurred with an incidence ≥1% in patients receiving JANUVIA™ (1.1%) and greater than in patients receiving placebo (0.4%).

Abnormal Hematologic and Clinical Chemistry Findings

The incidence of laboratory adverse experiences was similar in patients treated with JANUVIA™ 100 mg compared to patients treated with placebo. In most clinical studies, a slight decrease in alkaline phosphatase and small increases in uric acid and white blood cell count (due to an increase in neutrophils) were observed. In active comparator studies versus a sulfonylurea agent (glipizide) similar changes were seen in alkaline phosphatase and uric acid.

Mean Change from Baseline (Standard Error)				
Study	Treatment Group	Alkaline Phosphatase (IU/L)	Uric Acid (mg/dL)	WBC (cell/microl)
Placebo-controlled	Sitagliptin	-3.1 (0.4)	0.17 (0.04)	346.0 (64.3)
	Placebo	-1.3 (0.7)	0.05 (0.06)	142.4 (98.8)
Active-controlled	Sitagliptin	-5.7 (0.5)	0.21 (0.05)	207.8 (67.4)
	Glipizide	-3.4 (0.5)	0.20 (0.05)	86.0 (62.5)

Post-Marketing Adverse Drug Reactions

The following additional adverse reactions have been identified during post-marketing use of JANUVIA™. 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 include anaphylaxis, angioedema, rash, urticaria, and exfoliative skin conditions, including Stevens-Johnson syndrome.

DRUG INTERACTIONS

Overview

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.

Drug-Drug Interactions

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).

Metformin: Co-administration of multiple twice-daily doses of sitagliptin with metformin, an OCT substrate, did not meaningfully alter the pharmacokinetics of metformin or JANUVIA™ 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, were not meaningfully altered in subjects receiving multiple doses of sitagliptin. Clinically meaningful interactions would not be expected with other sulfonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glyburide, are primarily eliminated by CYP2C9. The effect of sulfonylureas on the pharmacokinetics of sitagliptin was not assessed.

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

Thiazolidinediones: Single-dose pharmacokinetics of rosiglitazone were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP2C8-mediated metabolism. Clinically meaningful interactions with pioglitazone are not expected because pioglitazone predominantly undergoes CYP2C8- or CYP3A4-mediated metabolism. The effect of thiazolidinediones on the pharmacokinetics of sitagliptin was not assessed.

Warfarin: Multiple daily doses of sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Since S(-) warfarin is primarily 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.

Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of JANUVIA™ daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma C_{max} by 18%. These increases are not considered likely to be clinically meaningful. No dosage adjustment of digoxin or JANUVIA™ is recommended.

Cyclosporine: A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Coadministration of a single 100-mg oral dose of JANUVIA™ and a single 600-mg oral dose of 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. No dosage adjustment for JANUVIA™ is recommended when co-administered with cyclosporine or other p-glycoprotein inhibitors (e.g., ketoconazole).

Drug-Food Interactions

There are no known interactions with food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

No studies of the effects of JANUVIA™ on the ability to drive and use machines have been performed. However, JANUVIA™ is not expected to affect the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations

JANUVIA™ can be taken with or without food.

Recommended Dose and Dosage Adjustment

The recommended dose of JANUVIA™ is 100 mg once daily.

Patients with Renal Insufficiency: Use of sitagliptin in patients with moderate or severe renal insufficiency including those with ESRD is not recommended.

Patients with Hepatic Insufficiency: Use of sitagliptin in patients with severe hepatic insufficiency is not recommended.

Geriatrics: No dosage adjustment is necessary for geriatric patients.

Pediatrics: There are no data available on the use of JANUVIA™ in patients younger than 18 years of age. Therefore, use of JANUVIA™ in pediatric patients is not recommended.

Missed Dose

If a dose of JANUVIA™ is missed, it should be taken as soon as the patient remembers. A double dose of JANUVIA™ should not be taken on the same day.

OVERDOSAGE

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

JANUVIA™ is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme that enhances incretin hormones. The DPP-4 inhibitors are a novel class of agents.

Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the

physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells, by intracellular signaling pathways involving cyclic AMP. Progressive beta-cell failure is a feature characterizing the pathogenesis of type 2 diabetes. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced.

In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. When blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. GLP-1 does not impair the normal glucagon response to hypoglycemia.

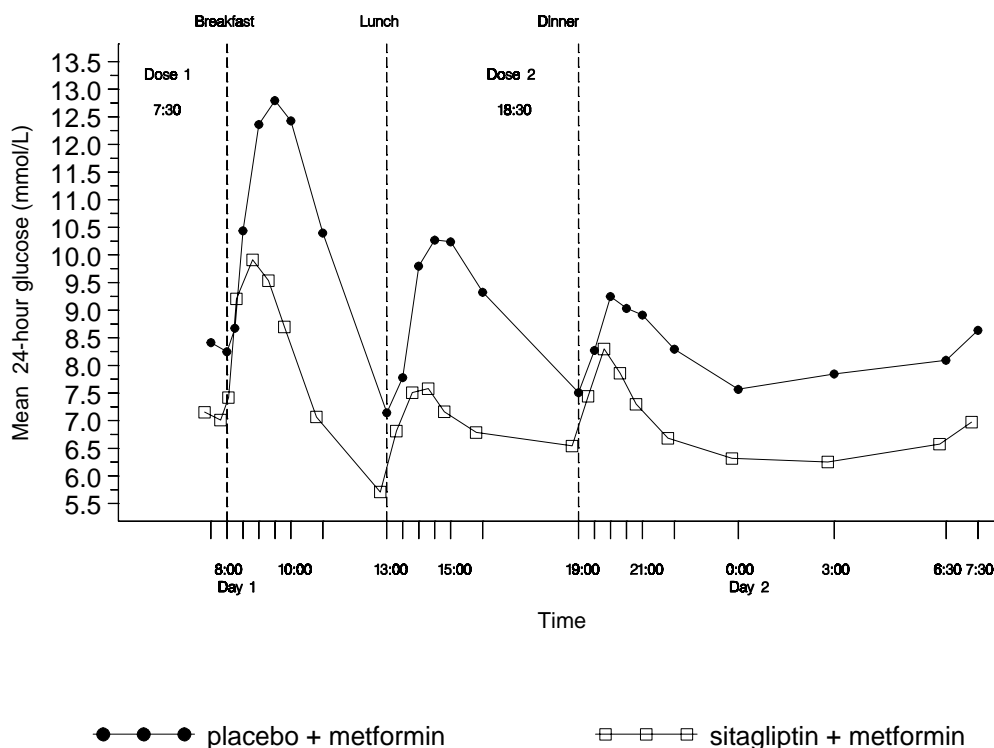
The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. In patients with type 2 diabetes with hyperglycemia, these changes in insulin and glucagon levels lead to lower hemoglobin A_{1c} (HbA_{1c}) and lower fasting and postprandial glucose concentrations. While sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4, it does not inhibit the closely-related enzymes DPP-8 or DPP-9. Inhibition of DPP-8 or DPP-9, but not DPP-4, is associated with toxicity in preclinical animal models and alteration of immune function in vitro.

Pharmacodynamics

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

In a study of patients with type 2 diabetes inadequately controlled on metformin monotherapy (N=26), glucose levels monitored throughout the day were significantly lower ($p<0.001$) in patients who received JANUVIA™ 100 mg per day in combination with metformin compared with patients who received placebo with metformin (see Figure 1).

Figure 1 - 24-hour plasma glucose profile after 4-week treatment with JANUVIA™ 100 mg daily with metformin or placebo with metformin



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

Cardiac Electrophysiology: In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of JANUVIA™ 100 mg, JANUVIA™ 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800-mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline at 3 hours postdose was 8.0 msec. This small increase was not considered to be clinically significant. At the 800-mg dose, peak sitagliptin plasma concentrations were approximately 11-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

Table 3 - Summary of sitagliptin's pharmacokinetic parameters in healthy volunteers

	C_{max} nM	t_½ (h)	AUC_{0-∞} μM•hr	Renal Clearance mL/min	Volume of distribution (L)*
Single oral dose (100 mg) mean	950	12.4	8.52	350	198

* Volume of distribution at steady state following an I.V. dose.

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

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

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

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

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

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

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

Special Populations and Conditions

Pediatrics: No studies with JANUVIA™ have been performed in pediatric patients.

Geriatrics: No dosage adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

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

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

Hepatic Insufficiency: In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% (90% CI: 1%, 46%) and 13% (90% CI: -9%, 42%), respectively, compared to healthy matched controls following administration of a single 100-mg dose of JANUVIA™.

Renal Insufficiency: An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency, and an approximately 4-fold increase was observed in patients with severe renal insufficiency and in patients with ESRD on hemodialysis, as compared to normal healthy control subjects.

STORAGE AND STABILITY

Store at room temperature (15°C to 30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Tablets JANUVIA™, 100 mg, are beige, round, film-coated tablets with “277” on one side. They are supplied in bottles of 30 and 100.

Each film-coated tablet of JANUVIA™ contains 128.5 mg of sitagliptin phosphate monohydrate, which is equivalent to 100 mg of free base.

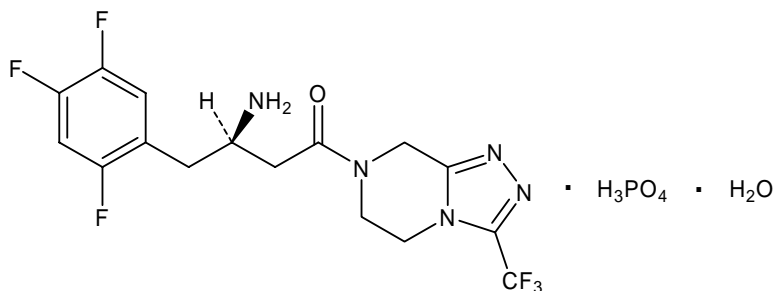
Each film-coated tablet of JANUVIA™ contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol (macrogol), talc, titanium dioxide, red iron oxide, and yellow iron oxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

- Common name: sitagliptin phosphate monohydrate
- Chemical name: 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.
- Molecular formula: $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$
- Molecular mass: 523.32
- Structural formula:



- Physicochemical properties: 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.

CLINICAL TRIALS

Study demographics and trial design

Table 4 - Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 1	Multicentre, randomized, double-blind, placebo-controlled	JANUVIA™ 100 mg once daily + \geq 1500 mg/day Metformin Or Placebo + \geq 1500 mg/day Metformin Oral 24-week	701	54.5 years (19-78)	Male: 400 Female: 301
Study 2	Multicentre, randomized, double-blind, with an active comparator	JANUVIA™ 100 mg/ day + \geq 1500 mg/day Metformin or Glipizide 5-20 mg /day + \geq 1500 mg/day Metformin Oral 52-week	1172	Male 23-79 Female 22-78	Male: 694 Female: 478

Study results

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

Sitagliptin in Combination with Metformin – Placebo-Controlled Study: A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA™ in combination with metformin. All patients were started on metformin monotherapy and the dose increased to at least 1500 mg per day. Patients were randomized to the addition of either 100 mg of JANUVIA™ or placebo, administered once daily. Patients with congestive heart failure requiring pharmacological treatment were excluded from this study.

In combination with metformin, JANUVIA™ provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo with metformin (Table 5). The improvement in HbA_{1c} was not affected by baseline HbA_{1c}, prior anti-hyperglycemic therapy, gender, age,

baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome (according to NCEP criteria), or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA-β). Body weight decreased from baseline in both treatment groups.

Table 5 - Glycemic parameters and body weight at final visit (24-week study) for JANUVIA™ in combination with metformin[†]

	JANUVIA 100 mg + Metformin	Placebo + Metformin
HbA_{1c} (%)	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 [‡])	-0.7 [§]	
Patients (%) achieving HbA _{1c} <7%	213 (47.0%)	41 (18.3%)
FPG (mmol/L)	N = 454	N = 226
Baseline (mean)	9.4	9.6
Change from baseline (adjusted mean [‡])	-0.9	0.5
Difference from placebo + metformin (adjusted mean [‡])	-1.4 [§]	
2-hour PPG (mmol/L)	N = 387	N = 182
Baseline (mean)	15.3	15.1
Change from baseline (adjusted mean [‡])	-3.4	-0.6
Difference from placebo + metformin (adjusted mean [‡])	-2.8 [§]	
Body Weight (kg) %	N = 399	N = 169
Baseline (mean)	86.9	87.6
Change from baseline (adjusted mean [‡])	-0.7	-0.6
Difference from placebo + metformin (adjusted mean [‡])	-0.1 [¶]	

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

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

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

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

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

Sitagliptin in Combination with Metformin - Active-Controlled (Sulfonylurea Agent)

Study: Long-term maintenance of effect was evaluated in a 52-week, double-blind, glipizide-controlled trial in patients with type 2 diabetes and inadequate glycemic control on metformin monotherapy at ≥1500 mg/day. In this study, patients were randomized to the addition of either JANUVIA™ 100 mg daily (N=588) or glipizide (N=584) for 52 weeks. Patients receiving glipizide were given an initial dosage of 5 mg/day and then electively titrated by the investigator to a target FPG of 6.1 mmol/L, without significant hypoglycemia, over the next 18 weeks. A maximum dosage of 20 mg/day was allowed to optimize glycemic control. Thereafter, the glipizide dose was to have been kept constant. The mean daily dose of glipizide after the titration period was 10.3 mg.

Both treatments resulted in a statistically significant improvement in glycemic control from baseline. After 52 weeks, the reduction from baseline in HbA_{1c} was 0.67% for JANUVIA™ 100 mg daily and 0.67% for glipizide, confirming the non-inferiority of JANUVIA™ compared to glipizide. The reduction in FPG was 0.6 mmol/L for JANUVIA™ and 0.4 mmol/L for glipizide. In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with JANUVIA™ relative to glipizide. The incidence of hypoglycemia in the JANUVIA™ group (4.9%) was significantly lower than that in the glipizide group (32.0%). Patients treated with JANUVIA™ exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs. +1.1 kg).

DETAILED PHARMACOLOGY

Sitagliptin was assessed for its ability to improve glucose tolerance in lean and diet-induced obese (DIO) mice following dextrose challenge and in diabetic (db/db) mice. In lean and DIO mice, single oral doses of sitagliptin reduced blood glucose levels in a dosage-dependent manner. Acute lowering of blood glucose was also demonstrated in diabetic db/db mice. A 2- to 3-fold increase in active GLP-1 was seen at the maximally effective dose of 1 mg/kg sitagliptin in lean mice. These results are consistent with the action of sitagliptin as an anti-hyperglycemic agent.

Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose, stimulate insulin biosynthesis and release, increase beta cell neogenesis, and decrease beta cell death. The effects on beta cell neogenesis and beta cell death have not been studied in humans.

TOXICOLOGY

Acute Toxicity

The approximate LD₅₀ of sitagliptin given orally to rats is >3000 mg/kg (maximum dose tested). This dose is equivalent to ≥200 times the human exposure based on the recommended daily adult human dose of 100 mg/day. In mice the approximate oral LD₅₀ of sitagliptin is 4000 mg/kg. This dose is equivalent to >385 times the human exposure based on recommended daily adult human dose of 100 mg/day.

Chronic Toxicity

The toxicity potential of sitagliptin was evaluated in a series of repeated dose toxicity studies of up to 53 weeks in dogs and up to 27 weeks in rats. In dogs administered sitagliptin orally at dosages of 2, 10 and 50 mg/kg/day, the no-observed effect level was 10 mg/kg/day (up to 6 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Treatment-related physical signs observed in the 50-mg/kg/day group included open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture. These signs were transient, slight in degree, and occurred with decreased incidence

during the course of the study. In addition, very slight to slight skeletal muscle degeneration was observed histologically in the 14- and 27-week toxicity studies at the 50-mg/kg/day dose. However, no skeletal muscle degeneration was found in the 53-week toxicity study, indicating the lack of reproducibility or progression of this change with increased duration of treatment. The 50-mg/kg/day dose in dogs resulted in systemic exposure values 26 times the human exposure at the recommended daily adult human dose of 100 mg/day. In rats, sitagliptin administered orally at dosages of up to 180 mg/kg/day (up to 23 times the human exposure based on the recommended daily adult human dose of 100 mg/day), no significant toxicity was observed. The only drug-related effect observed was postdose salivation, likely related to poor palatability of the drug, at doses of 60 mg/kg/day and 180mg/kg/day.

The treatment-related changes noted in animals do not suggest any clinical concerns at the recommended therapeutic dosages in humans.

Carcinogenicity

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 hepatic adenomas and carcinomas in the high-dose males and hepatic carcinomas in the high-dose females. This dose in rats results in approximately 58 times the human exposure based on the recommended daily adult human dose of 100 mg/day. This dose level was associated with hepatotoxicity in rats. The no-observed effect level for induction of hepatic neoplasia was 150 mg/kg/day, approximately 19-fold the human exposure at the 100-mg recommended dose. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumors in rats was likely secondary to chronic hepatic toxicity at this high dose. The clinical significance of these findings for humans is unknown.

A two-year carcinogenicity study was conducted in male and female mice at oral doses of 50, 125, 250, and 500 mg/kg/day. Sitagliptin did not increase tumor incidence in mice in any organ at doses up to 500 mg/kg/day (approximately 68 times the human exposure based on the recommended daily adult human dose of 100 mg/day).

Mutagenesis

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

Reproduction

No adverse effects upon fertility were observed in male and female rats given sitagliptin orally at doses up to 1000 mg/kg daily (up to approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day) prior to and throughout mating.

Development

Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg or in rabbits given up to 125 mg/kg during organogenesis (up to 32 and 22 times the human exposure based on the recommended daily adult human dose of 100 mg/day). A slight, treatment-related increased incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) was observed in the offspring of rats at oral doses of 1000 mg/kg/day (approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day). The no-observed effect level for developmental effects was 250 mg/kg/day (32 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Treatment-related decreases in the mean preweaning body weight of both sexes and postweaning body weight gain of male animals was observed in offspring of rats at oral doses of 1000 mg/kg.

REFERENCES

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2. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* 2006;29(12):2638-43. [Ref. 5.4: 1]
3. Drucker DJ. Development of glucagon-like peptide-1-based pharmaceuticals as therapeutic agents for the treatment of diabetes. *Curr Pharm Des* 2001;7(14):1399-412. [Ref. 5.4: 2]
4. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab* 2007;9(2):194-205. [Ref. 5.4: 3]

PART III: CONSUMER INFORMATION

JANUVIA™
sitagliptin tablets
(as sitagliptin phosphate monohydrate)

This leaflet is part III of a three-part "Product Monograph" published when JANUVIA™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about JANUVIA™. Contact your physician or pharmacist if you have any questions about the drug.

Please read this information carefully before you start to take your medicine, even if you have just refilled your prescription. Some of the information may have changed.

Remember that your physician has prescribed this medicine only for you. Never give it to anyone else.

ABOUT THIS MEDICATION

What the medication is used for:

- JANUVIA™ is used in combination with metformin to improve blood sugar levels in adult patients with type 2 diabetes mellitus in addition to diet and exercise.

What it does:

JANUVIA™ is a member of a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors). JANUVIA™ helps to improve the levels of insulin when blood sugar level is high, especially after a meal. JANUVIA™ also helps to decrease the amount of sugar made by the body. JANUVIA™ is unlikely to cause low blood sugar (hypoglycemia).

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and/or does not use the insulin that your body produces as well as it should. When this happens, sugar (glucose) builds up in the blood. This can lead to serious problems.

When it should not be used:

Do not take JANUVIA™ if you are allergic to any of the ingredients in JANUVIA™.

What the medicinal ingredient is:
 sitagliptin phosphate monohydrate

What the important non-medicinal ingredients are:

Each film-coated tablet of JANUVIA™ contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and yellow iron oxide.

What dosage forms it comes in:

Tablets. Each tablet contains 100 mg sitagliptin.

WARNINGS AND PRECAUTIONS

BEFORE you use JANUVIA™ talk to your physician or pharmacist if:

- you have type 1 diabetes.
- you have or have had diabetic ketoacidosis (increased ketones in the blood or urine).
- you have or have had an allergic reaction to JANUVIA™.
- you have congestive heart failure.
- you have or have had kidney problems.
- you have liver problems.
- you are pregnant or plan to become pregnant. JANUVIA™ is not recommended for use during pregnancy.
- you are breast-feeding or plan to breast-feed. It is not known if JANUVIA™ passes into breast milk.

JANUVIA™ is not recommended for use in children under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Tell your physician or pharmacist about all the medicines you take. This includes prescription and non-prescription medicines, and herbal supplements.

PROPER USE OF THIS MEDICATION

Take JANUVIA™ exactly as your physician has prescribed.

Usual dose:

100 mg once daily by mouth with or without food.

Overdose:

If you take more than the prescribed dosage of JANUVIA™, contact your physician or poison control centre immediately.

Missed Dose:

If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose of JANUVIA™ on the same day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, JANUVIA™ may cause side effects.

The most common side effects of JANUVIA™ include: stuffy or runny nose and sore throat.

Tell your physician or pharmacist if you develop any unusual side effects, or any of the above side effects that do not go away or gets worse.

The following additional side effects have been reported in general use with JANUVIA™:

- Allergic reactions, which may be serious, including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing. If you have an allergic reaction, stop taking JANUVIA™ and call your physician right away. Your physician may prescribe a medication to treat your allergic reaction and a different medication for your diabetes.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / Effects		Talk with your physician or pharmacist		Stop taking drug and call your physician or pharmacist
		Only if severe	In all cases	
Rare	Allergic reactions including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.			√

This is not a complete list of side effects. For any unexpected effects while taking JANUVIA™, contact your physician or pharmacist.

HOW TO STORE IT

Store at room temperature (15°C to 30°C).

Keep JANUVIA™ and all medicines safely away from children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 1-866-234-2345
 Toll-free fax: 1-866-678-6789
 By email: cadrmp@hc-sc.gc.ca

By regular mail:
 Canada Vigilance National Office
 Marketed Health Products Safety and Effectiveness
 Information Division
 Marketed Health Products Directorate
 Tunney's Pasture, AL 0701C
 Ottawa ON K1A 0K9

or Merck Frosst Canada Ltd. by:

Toll-free telephone: 1-800-567-2594
 Toll-free fax: 1-877-428-8675
 By regular mail:
 Merck Frosst Canada Ltd.
 P.O. Box 1005
 Pointe-Claire - Dorval, QC H9R 4P8

NOTE: Before contacting Health Canada or Merck Frosst, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
<http://www.merckfrosst.com>
 or by contacting the sponsor, Merck Frosst Canada Ltd., at: 1-800-567-2594.

This leaflet was prepared by Merck Frosst Canada Ltd.

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