PRODUCT CIRCULAR

Tablet
JANUVIA®
(*sitagliptin phosphate*, MSD)

جنوويا®

I. THERAPEUTIC CLASS

JANUVIA* (*sitagliptin phosphate*) is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, *sitagliptin* increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. This mechanism is unlike the mechanism seen with sulfonylureas; sulfonylureas cause insulin release even when glucose levels are low, which can lead to sulfonylurea-induced hypoglycemia in patients with type 2 diabetes and in normal subjects. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. *Sitagliptin* differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

II. INDICATIONS

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

Combination with Metformin
JANUVIA is also indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin as initial therapy the single agent alone, with diet and exercise, does not provide adequate glycemic control.

Combination with a Sulfonylurea
JANUVIA is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a sulfonylurea when treatment with the single agent alone, with diet and exercise, does not provide adequate glycemic control.

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

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

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

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

III. DOSAGE AND ADMINISTRATION

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

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

Patients with Renal Insufficiency

For patients with mild renal insufficiency (creatinine clearance [CrCl] ≥50 mL/min, approximately corresponding to serum creatinine levels of ≤1.7 mg/dL in men and ≤1.5 mg/dL in women), no dosage adjustment for JANUVIA is required.

JANUVIA 100mg is not indicated in patients with moderate to severe renal insufficiency (CrCl <50mL/min, approximately corresponding to serum creatinine levels of >1.7mg/dL in men and >1.5mg/dL in women)

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

IV. CONTRAINDICATIONS

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

V. PRECAUTIONS

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

Use in Patients with Renal Insufficiency: JANUVIA is renally excreted. To achieve plasma concentrations of JANUVIA similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal insufficiency, as well as in ESRD patients requiring hemodialysis or peritoneal dialysis. (See **DOSAGE AND ADMINISTRATION**, *Patients with Renal Insufficiency*.)

Hypoglycemia in Combination with a Sulfonylurea or with Insulin: In clinical trials of JANUVIA as monotherapy and as part of combination therapy with agent known to cause hypoglycemia (i.e. metformin or pioglitazone), rates of hypoglycemia reported with JANUVIA were similar to rates in patients taking placebo. As is typical with other antihyperglycemic agents, when JANUVIA was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of sulfonylurea- or insulin-induced hypoglycemia was increased over that of placebo (see **SIDE EFFECTS**). Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia, a lower dose of sulfonylurea or insulin may be considered (see **DOSAGE AND ADMINISTRATION**).

Hypersensitivity Reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with JANUVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA, assess for other potential causes for the event, and institute alternative treatment for diabetes. (See **CONTRAINDICATIONS** and **SIDE EFFECTS**, *Postmarketing Experience*.)

VI. PREGNANCY

Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg or in rabbits given up to 125 mg/kg during organogenesis (up to 32 and 22 times, respectively, the human exposure based on the recommended daily adult human dose of 100 mg/day). In rats, a slight increase in the incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) was observed at oral doses of 1000 mg/kg/day (approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Slight decreases in mean preweaning body weights of both sexes and postweaning body weight gains of males were observed in the offspring of rats given oral dose of 1000 mg/kg/day. However, animal reproduction studies are not always predictive of the human response.

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

VII. NURSING MOTHERS

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

VIII. PEDIATRIC USE

Safety and effectiveness of JANUVIA in pediatric patients under 18 years have not been established.

IX. USE IN THE ELDERLY

In clinical studies, the safety and effectiveness of JANUVIA in the elderly (≥65 years) were comparable to those seen in younger patients (<65 years). No dosage adjustment is required based on age. Elderly patients are more likely to have renal insufficiency; as with other patients, dosage adjustment may be

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required in the presence of significant renal insufficiency (see **DOSAGE AND ADMINISTRATION**, *Patients with Renal Insufficiency*).

X. DRUG INTERACTIONS

In drug interaction studies, *sitagliptin* did not have clinically meaningful effects on the pharmacokinetics of the following: metformin, rosiglitazone, glyburide, simvastatin, warfarin, and oral contraceptives. Based on these data, *sitagliptin* does not inhibit CYP isozymes CYP3A4, 2C8, or 2C9. Based on *in vitro* data, *sitagliptin* is also not expected to inhibit CYP2D6, 1A2, 2C19 or 2B6 or to induce CYP3A4.

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

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. Medications assessed were those that are commonly administered to patients with type 2 diabetes including cholesterol-lowering agents (e.g., statins, fibrates, ezetimibe), anti-platelet agents (e.g., clopidogrel), antihypertensives (e.g., ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (e.g., naproxen, diclofenac, celecoxib), anti-depressants (e.g., bupropion, fluoxetine, sertraline), antihistamines (e.g., cetirizine), proton-pump inhibitors (e.g., omeprazole, lansoprozole), and medications for erectile dysfunction (e.g., sildenafil).

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C_{max}, 18%) of digoxin with the co-administration of *sitagliptin*. These increases are not considered likely to be clinically meaningful. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or JANUVIA is recommended.

The AUC and C_{max} of *sitagliptin* were increased approximately 29% and 68%, respectively, in subjects with co-administration of a single 100-mg oral dose of JANUVIA and a single 600-mg oral dose of cyclosporine, a potent probe inhibitor of p-glycoprotein. The observed changes in *sitagliptin* pharmacokinetics are not considered likely to be clinically meaningful. No dosage adjustment for JANUVIA is recommended when co-administered with cyclosporine or other p-glycoprotein inhibitors (e.g., ketoconazole).

XI. SIDE EFFECTS

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

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

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

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

Add-on Combination with a Sulfonylurea: In a 24-week placebo-controlled study of JANUVIA 100 mg in combination with glimepiride or with glimepiride and metformin (JANUVIA, N=222; placebo, N=219), the drug-related adverse reaction reported in ≥1% of patients treated with JANUVIA and more commonly than in patients treated with placebo was hypoglycemia (JANUVIA, 9.5%; placebo, 0.9%).

Add-on Combination with Metformin and a PPARγ Agonist: In a placebo-controlled study of JANUVIA 100 mg in combination with metformin and rosiglitazone (JANUVIA, N=170; placebo, N=92), the drug-related adverse reactions reported through the primary time point at Week 18 in ≥1% of patients treated with JANUVIA and more commonly than in patients treated with placebo were: headache (JANUVIA, 2.4%; placebo, 0.0%), diarrhea (1.8%, 1.1%), nausea (1.2%, 1.1%), hypoglycemia (1.2%, 0.0%), and vomiting (1.2%, 0.0%). Through Week 54, the drug-related adverse reactions reported in ≥1% of patients treated with JANUVIA and more commonly than in patients treated with placebo were: headache (2.4%, 0.0%), hypoglycemia (2.4%, 0.0%), upper respiratory tract infection (1.8%, 0.0%), nausea (1.2%, 1.1%), cough (1.2%, 0.0%), fungal skin infection (1.2%, 0.0%), peripheral edema (1.2%, 0.0%), and vomiting (1.2%, 0.0%).

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

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

Add-on Combination with Insulin: In a 24-week placebo-controlled study of JANUVIA 100 mg in combination with insulin (with or without metformin), the drug-related adverse reactions reported in ≥1% of patients treated with JANUVIA (N=322) and more commonly than in patients treated with placebo (N=319) were: hypoglycemia (JANUVIA, 9.6%; placebo, 5.3%), influenza (1.2%, 0.3%), and headache (1.2%, 0.0%).

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

Postmarketing Experience:
The following additional adverse reactions have been identified during postmarketing 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, cutaneous vasculitis, and exfoliative skin conditions, including Stevens-Johnson syndrome (see **CONTRAINDICATIONS** and **PRECAUTIONS**, *Hypersensitivity Reactions*); upper respiratory tract infection; nasopharyngitis; pancreatitis.

XIa. Laboratory Test Findings

The incidence of laboratory adverse experiences was similar in patients treated with JANUVIA 100 mg compared to patients treated with placebo. Across clinical studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to an increase in neutrophils. This observation was seen in most but not all studies. These changes in laboratory parameters are not considered to be clinically relevant.

XII. OVERDOSAGE

During controlled clinical trials in healthy subjects, single doses of up to 800 mg JANUVIA were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg JANUVIA (see **CLINICAL PHARMACOLOGY**, ***Pharmacodynamics***, *Cardiac Electrophysiology*). There is no experience with doses above 800 mg in humans. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with JANUVIA with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

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

XIII. AVAILABILITY

Tablets JANUVIA (sitagliptin phosphate, MSD) is available in the strength of 100 mg pack of (2 x 14's strip)

Each film coated tablet contains:
128.5 mg of Sitagliptin Phosphate Monohydrate, MSD equivalent to 100 mg Sitagliptin.

PAK-JAN-T-032009a

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Italy – Lic. No. AM-38/2004

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