PRODUCT CIRCULAR

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JANUMET®
(sitagliptin phosphate/metformin HCl, MSD)
Tablets

I. THERAPEUTIC CLASS

JANUMET

JANUMET[1] (sitagliptin phosphate/metformin HCl) combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Sitagliptin phosphate

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.

Metformin hydrochloride

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **PRECAUTIONS**, *Metformin hydrochloride*) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion

remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

II. INDICATIONS

JANUMET is indicated as initial therapy in patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise do not provide adequate glycemic control.

JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus inadequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

JANUMET is indicated as part of triple combination therapy with a sulfonylurea as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled with any two of the three agents: metformin, sitagliptin, or a sulfonylurea.

JANUMET is indicated as part of triple combination therapy with a PPARγ agonist (i.e., thiazolidinediones) as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled with any two of the three agents: metformin, sitagliptin, or a PPARγ agonist.

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

III. DOSAGE AND ADMINISTRATION

General:
The dosage of antihyperglycemic therapy with JANUMET should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin.

JANUMET should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects associated with metformin.

Dosing Recommendations:
The starting dose of JANUMET should be based on the patient's current regimen. JANUMET should be given twice daily with meals. The following doses are available:

50 mg sitagliptin/500 mg metformin hydrochloride

50 mg sitagliptin/1000 mg metformin hydrochloride

As initial therapy:

For patients with type 2 diabetes mellitus, whose hyperglycemia is inadequately controlled with diet and exercise alone, the recommended starting dose of JANUMET is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily. Patients may be titrated up to 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily.

For patients inadequately controlled on metformin monotherapy:
For patients inadequately controlled on metformin alone, the usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken.

For patients inadequately controlled on sitagliptin monotherapy:
For patients inadequately controlled on sitagliptin alone, the usual starting dose of JANUMET is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily. Patients may be titrated up to 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily. Patients taking sitagliptin monotherapy dose-adjusted for renal insufficiency should not be switched to JANUMET (see **CONTRAINDICATIONS)**.

For patients switching from co-administration of sitagliptin and metformin:
For patients switching from co-administration of sitagliptin and metformin, JANUMET may be initiated at the dose of sitagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with any two of the following three antihyperglycemic agents: sitagliptin, metformin or a sulfonylurea:
The usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. Patients currently on or initiating a sulfonylurea may require lower sulfonylurea doses to reduce the risk of sulfonylurea-induced hypoglycemia (see **PRECAUTIONS**).

For patients inadequately controlled on dual combination therapy with any two of the following three antihyperglycemic agents: sitagliptin, metformin or a PPARγ agonist (i.e. thiazolidinediones):
The usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered.

For patients inadequately controlled on dual combination therapy with any two of the following three antihyperglycemic agents: sitagliptin, metformin or insulin:
The usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. Patients currently on or initiating insulin therapy may require lower doses of insulin to reduce the risk of hypoglycemia (see **PRECAUTIONS**).

No studies have been performed specifically examining the safety and efficacy of JANUMET in patients previously treated with other oral antihyperglycemic agents and switched to JANUMET. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

IV. CONTRAINDICATIONS

JANUMET (*sitagliptin phosphate/metformin HCl*) is contraindicated in patients with:

1. Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females], or abnormal creatinine clearance, which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
2. Known hypersensitivity to sitagliptin phosphate, metformin hydrochloride or any other component of JANUMET (See **PRECAUTIONS**, *Sitagliptin phosphate,* Hypersensitivity Reactions and **SIDE EFFECTS**, *Postmarketing Experience*).

3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

JANUMET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see **PRECAUTIONS**; *Metformin hydrochloride*).

V. PRECAUTIONS

JANUMET

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

Pancreatitis: In postmarketing experience there have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis (see **SIDE EFFECTS**, *Postmarketing Experience*), in patients taking sitagliptin. Because these reports are made voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin. If pancreatitis is suspected, JANUMET and other potentially suspect medicinal products should be discontinued.

Monitoring of renal function: Metformin and sitagliptin are known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive JANUMET. In patients with advanced age, JANUMET should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging can be associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly.

Before initiation of therapy with JANUMET and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and JANUMET discontinued if evidence of renal impairment is present.

Hypoglycemia in Combination with a Sulfonylurea or with Insulin: As is typical with other antihyperglycemic agents, when the combination of sitagliptin and metformin was used with, a sulfonylurea or insulin, medications known to cause hypoglycemia, the incidence of sulfonylurea- or insulin-induced hypoglycemia was increased over that observed when the combination of placebo and metformin, was used with a sulfonylurea or insulin *(*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**).

Sitagliptin phosphate

Hypoglycemia in Combination with a Sulfonylurea or with Insulin: In clinical trials of sitagliptin as monotherapy and as part of combination therapy with agents not known to cause hypoglycemia (i.e., metformin or a PPARγ agonist (thiazolidinedione), rates of hypoglycemia reported with sitagliptin were similar to rates in patients taking placebo. As typical with other antihyperglycemic agents, when sitagliptin 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 sitagliptin, one of the components of JANUMET. 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 sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUMET, assess for other potential causes for the event, and institute alternative treatment for diabetes. (See **CONTRAINDICATIONS** and **SIDE EFFECTS**, *Postmarketing Experience*.)

Metformin hydrochloride

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET (s*itagliptin phosphate/metformin HCl*); when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Such management often results in prompt reversal of symptoms and recovery (see **CONTRAINDICATIONS**).

Hypoglycemia: Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs.

Use of concomitant medications that may affect renal function or metformin disposition: Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **DRUG INTERACTIONS**, *Metformin hydrochloride*), should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see **CONTRAINDICATIONS**). Therefore, in patients in whom any such study is planned, JANUMET should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states: Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on JANUMET therapy, the drug should be promptly discontinued.

Surgical procedures: Use of JANUMET should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving JANUMET.

Impaired hepatic function: Since impaired hepatic function has been associated with some cases of lactic acidosis, JANUMET should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels: In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in

patients on JANUMET and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes: A patient with type 2 diabetes previously well controlled on JANUMET who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, JANUMET must be stopped immediately and other appropriate corrective measures initiated.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold JANUMET and temporarily administer insulin. JANUMET may be reinstituted after the acute episode is resolved.

VI. PREGNANCY

JANUMET

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

No animal studies have been conducted with the combined products in JANUMET to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

Sitagliptin phosphate

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.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

VII. NURSING MOTHERS

No studies in lactating animals have been conducted with the combined components of JANUMET. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin is excreted in human milk. Therefore, JANUMET should not be used by a woman who is nursing.

VIII. PEDIATRIC USE

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

IX. USE IN THE ELDERLY

JANUMET

Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUMET should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function (See **PRECAUTIONS,** Monitoring of Renal Function).

Sitagliptin phosphate

In clinical studies, the safety and effectiveness of sitagliptin in the elderly (≥65 years,) were comparable to those seen in younger patients (<65 years).

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, Metformin should only be used in patients with normal renal function (see **CONTRAINDICATIONS**).

X. DRUG INTERACTIONS

Sitagliptin and metformin

Co-administration of multiple doses of sitagliptin (50 mg b.i.d.) and metformin (1000 mg b.i.d.) did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

Pharmacokinetic drug interaction studies with JANUMET have not been performed; however, such studies have been conducted with the individual components of JANUMET, sitagliptin and metformin.

Sitagliptin phosphate

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.

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on sitagliptin pharmacokinetics. Medications assessed were those that are commonly administered to patients with type 2 diabetes including 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, lansoprazole), 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 to be clinically meaningful. Patients receiving digoxin should be monitored appropriately. 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 to be clinically meaningful.

Metformin hydrochloride

Glyburide: In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than

when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JANUMET and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.
Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JANUMET the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

XI. SIDE EFFECTS

In placebo-controlled clinical trials, in patients with type 2 diabetes mellitus, the combination of sitagliptin and metformin was generally well tolerated. The overall incidence of side effects reported in patients receiving the combination of sitagliptin and metformin was similar to that reported in patients receiving the combination of placebo and metformin.

Combination Therapy with Sitagliptin and Metformin

Initial Therapy

In a 24-week placebo-controlled factorial study of initial therapy with sitagliptin 50 mg twice daily in combination with metformin at 500 or 1000 mg twice daily, the drug-related adverse reactions

reported in ≥1% of patients receiving combination therapy (and greater than in patients receiving placebo) are shown in Table 1.

Table 1
Initial Therapy with Combination of Sitagliptin and Metformin:
Drug-Related Adverse Reactions Reported in ≥1% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)†

	Number of Patients (%)			
	Placebo	**Sitagliptin 100 mg q.d.**	**Metformin 500 or 1000 mg b.i.d. ††**	**Sitagliptin 50 mg b.i.d. + Metformin 500 or 1000 mg b.i.d. ††**
	N = 176	**N = 179**	**N = 364**	**N = 372**
Diarrhea	2 (1.1)	0 (0.0)	12 (3.3)	13 (3.5)
Nausea	1 (0.6)	0 (0.0)	9 (2.5)	6 (1.6)
Dyspepsia	0 (0.0)	0 (0.0)	4 (1.1)	5 (1.3)
Flatulence	0 (0.0)	0 (0.0)	2 (0.5)	5 (1.3)
Vomiting	0 (0.0)	0 (0.0)	1 (0.3)	4 (1.1)
Headache	0 (0.0)	1 (0.6)	4 (1.1)	5 (1.3)
Hypoglycemia	0 (0.0)	1 (0.6)	2 (0.5)	4 (1.1)

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

Add-on Combination Therapy to Metformin

In a 24-week placebo-controlled study of sitagliptin added to ongoing metformin therapy, 464 patients on metformin were treated with sitagliptin 100 mg once daily and 237 patients were given placebo with metformin. The only drug-related adverse reaction reported that occurred with an incidence of ≥1% and higher than placebo in patients receiving sitagliptin and metformin was nausea (100 mg sitagliptin and metformin, 1.1%; placebo and metformin, 0.4%).

Hypoglycemia and Gastrointestinal Adverse Experiences

In the placebo-controlled studies of combination therapy with sitagliptin and metformin, the incidence of hypoglycemia (regardless of investigator assessment of causality) reported in patients treated with the combination of sitagliptin and metformin was similar to that reported for patients treated with metformin and placebo. The incidences of pre-specified gastrointestinal adverse experiences in patients treated with the combination of sitagliptin and metformin were similar to those reported for patients treated with metformin alone. See Table 2.

Table 2
Hypoglycemia and Pre-specified Gastrointestinal Intestinal Adverse Experiences (Regardless of Investigator Assessment of Causality) Reported in Patients Receiving Combination Therapy†

	Number of Patients (%)					
	Study of Sitagliptin and Metformin as Initial Therapy				**Study of Sitagliptin as Add-on to Metformin**	
	Placebo	**Sitagliptin 100 mg q.d.**	**Metformin 500 or 1000 mg b.i.d. ††**	**Sitagliptin 50 mg b.i.d. + Metformin 500 or 1000 mg b.i.d. ††**	**Placebo and Metformin ≥1500 mg daily**	**Sitagliptin 100 mg q.d. and Metformin ≥1500 mg daily**
	N = 176	**N = 179**	**N = 364**	**N = 372**	**N= 237**	**N= 464**

Hypoglycemia	1 (0.6)	1 (0.6)	3 (0.8)	6 (1.6)	5 (2.1)	6 (1.3)
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)	6 (2.5)	11 (2.4)
Nausea	2 (1.1)	2 (1.1)	20 (5.5)	18 (4.8)	2 (0.8)	6 (1.3)
Vomiting	1 (0.6)	0 (0.0)	2 (0.5)	8 (2.1)	2 (0.8)	5 (1.1)
Abdominal Pain†	4 (2.3)	6 (3.4)	14 (3.8)	11(3.0)	9 (3.8)	10 (2.2)

† In the study of initial therapy, Abdominal Discomfort was included with Abdominal Pain.
†† Data pooled for the patients given the lower and higher doses of metformin.

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

Sitagliptin in Combination with Metformin and a Sulfonylurea

In a 24-week placebo-controlled study of sitagliptin 100 mg daily added to ongoing combination treatment with glimepiride ≥4 mg daily and metformin ≥1500 mg daily, the drug-related adverse reactions reported in ≥1% of patients treated with sitagliptin (N=116) and more commonly than in patients treated with placebo (N=113) were hypoglycemia (sitagliptin, 13.8%; placebo, 0.9%) and constipation (1.7%, 0.0%).

Sitagliptin in Combination with Metformin and a PPARγ Agonist

In a placebo-controlled study of sitagliptin 100 mg daily added to ongoing combination treatment with metformin and rosiglitazone, the drug-related adverse reactions reported through the primary time point at Week 18 in ≥1% of patients treated with sitagliptin (N=170) and more commonly than in patients treated with placebo (N=92) were: headache (sitagliptin, 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 sitagliptin 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%).

Sitagliptin in Combination with Metformin and Insulin

In a 24-week placebo-controlled study of sitagliptin 100 mg added to ongoing combination treatment with metformin ≥1500 mg daily and insulin, the only drug-related adverse reaction reported in ≥1% of patients treated with sitagliptin (N=229) and more commonly than in patients treated with placebo (N=233) was hypoglycemia (sitagliptin, 10.9%; placebo, 5.2%).

Pancreatitis

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). (See **PRECAUTIONS**, *Pancreatitis*).

With the combination of sitagliptin and metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed.

Established Adverse Reactions with Sitagliptin

There were no drug-related adverse reactions reported that occurred with an incidence of ≥1% in patients receiving sitagliptin.

*Established Adverse Reactions with Metformin **
CNS: Headache
GI: Abdominal bloating, anorexia, diarrhea, flatulence, metallic taste, nausea, vomiting
HFME: Megaloblastic anemia (impaired vitamin B12 absorption)
METAB: Hypoglycemia (rare); lactic acidosis (diarrhea; severe muscle pain, cramping; shallow and fast breathing, unusual tiredness and weakness, unusual sleepiness)
SKIN: Dermatitis, rash.

Postmarketing Experience:

Additional adverse reactions have been identified during postmarketing use of JANUMET or sitagliptin, one of the components of JANUMET. These reactions have been reported when JANUMET or sitagliptin have been used alone and/or in combination with other antihyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome (see **CONTRAINDICATIONS** and **PRECAUTIONS**, *Sitagliptin phosphate*, Hypersensitivity Reactions); acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see **PRECAUTIONS**, Pancreatitis); worsening renal function, including acute renal failure (sometimes requiring dialysis); upper respiratory tract infection; nasopharyngitis; constipation; vomiting; headache; arthralgia; myalgia; pain in extremity; back pain.

XIa. Laboratory Test Findings

Sitagliptin phosphate

The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin and metformin compared to patients treated with placebo and metformin. 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 a small increase in neutrophils. This observation was seen in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant.

Metformin hydrochloride

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation (see **PRECAUTIONS**, *Metformin hydrochloride*).

XII. OVERDOSAGE

Sitagliptin phosphate

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin 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 sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin 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.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **PRECAUTIONS**, *Metformin hydrochloride*). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

XIII. AVAILABILITY

JANUMET (sitagliptin phosphate/metformin HCl) Tablet is available as:

- 50/500 mg in blister pack of 14 Tablets (2 x 7's). Each film coated tablet contains 64.25 mg sitagliptin phosphate monohydrate (equivalent to 50 mg sitagliptin) & 500 mg metformin HCl.

- 50/1000 mg in blister pack of 14 Tablets (2 x 7's). Each film coated tablet contains 64.25 mg sitagliptin phosphate monohydrate (equivalent to 50 mg sitagliptin) & 1000 mg metformin HCl.

Manufactured for:
Merck Sharp & Dohme Corp.,
a subsidiary of MERCK & CO. INC.,
Whitehouse Station, NJ 08889, USA

By:
Patheon Puerto Rico, Inc.,
Manati, Puerto Rico, 00674.
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