JANUMET® XR
(sitagliptin phosphate/metformin HCl extended-release, MSD)
Tablets

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate.

If acidosis is suspected, JANUMET® XR should be discontinued and the patient hospitalized immediately. *[See PRECAUTIONS.]*

I. THERAPEUTIC CLASS

JANUMET XR (sitagliptin phosphate/metformin HCl extended-release) 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.

JANUMET XR tablets consist of sitagliptin and an extended-release formulation of metformin.

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

JANUMET XR is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

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

JANUMET XR is indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in patients when insulin and metformin alone do not provide adequate glycemic control.

Important Limitations of Use

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

JANUMET XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUMET XR (see **PRECAUTIONS**).

III. DOSAGE AND ADMINISTRATION

General:

The dosage of antihyperglycemic therapy with JANUMET XR 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 and 2000 mg metformin.

JANUMET XR should be given once daily with a meal preferably in the evening. The dose should be escalated gradually to reduce the gastrointestinal (GI) side effects due to metformin. Additionally, administration of JANUMET XR with food enhances plasma concentrations of metformin. To preserve the modified-release properties, the tablets must not be split, broken, crushed, or chewed before swallowing. There have been reports of incompletely dissolved JANUMET XR tablets being eliminated in the feces. It is not known whether this material seen in feces contains active drug. If a patient reports repeatedly seeing tablets in feces, the healthcare provider should assess adequacy of glycemic control.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements.

Dosing Recommendations:

The starting dose of JANUMET XR should be based on the patient's current regimen.

In patients already treated with metformin, the starting dose of JANUMET XR should include the equivalent daily dose of metformin while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin.

JANUMET XR should be given once daily with a meal preferably in the evening. JANUMET XR tablets are available in the following strengths:

50 mg sitagliptin/500 mg extended-release metformin hydrochloride
50 mg sitagliptin/1000 mg extended-release metformin hydrochloride
100 mg sitagliptin/1000 mg extended-release metformin hydrochloride

For patients using the 50 mg sitagliptin/500 mg metformin hydrochloride extended-release tablet or the 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablet, two tablets should be taken together once daily. The 100 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablet should be taken as a single tablet once daily.

Patients inadequately controlled with diet and exercise alone:

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient with type 2 diabetes mellitus inadequately controlled with diet and exercise alone, the recommended total daily starting dose of JANUMET XR is 100 mg sitagliptin and 1000 mg metformin hydrochloride. Patients with inadequate glycemic control on this dose can be titrated gradually to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily metformin dose of 2000 mg.

For patients inadequately controlled on metformin monotherapy:

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient inadequately controlled on metformin alone, the recommended total daily starting dose of JANUMET XR is 100 mg sitagliptin and the previously prescribed dose of metformin.

For patients inadequately controlled on sitagliptin monotherapy:
If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient inadequately controlled on sitagliptin alone, the recommended starting dose of JANUMET XR is 100 mg sitagliptin and 1000 mg metformin hydrochloride. The metformin dose can be titrated as needed to achieve glycemic control. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. Patients taking sitagliptin monotherapy dose-adjusted for renal impairment should not be switched to JANUMET XR (see **CONTRAINDICATIONS**).

For patients switching from coadministration of sitagliptin and metformin:
For patients switching from coadministration of sitagliptin and metformin, JANUMET XR may be initiated at the previously prescribed dose of sitagliptin and metformin.

For patients inadequately controlled on dual combination therapy with any two of the following three antihyperglycemic agents: sitagliptin, metformin or a sulfonylurea:
If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate in this setting, the usual starting dose of JANUMET XR should provide 100 mg total daily dose of sitagliptin. 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 insulin and metformin:
The usual starting dose of JANUMET XR should provide 100 mg total daily dose of sitagliptin. 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 XR in patients previously treated with other oral antihyperglycemic agents and switched to

JANUMET XR. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

Recommendations for use in renal impairment:
Assess renal function prior to initiation of JANUMET XR and periodically thereafter.

JANUMET XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2. Discontinue JANUMET XR if the patient's eGFR later falls below 30 mL/min/1.73 m^2 (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

Initiation of JANUMET XR in patients with an eGFR ≥ 30 mL/min/1.73 m^2 and < 45 mL/min/1.73 m^2 is not recommended. In patients taking JANUMET XR whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy and limit dose of the sitagliptin component to 50 mg once day.

Discontinuation for iodinated contrast imaging procedures:
Discontinue JANUMET XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR ≥ 30 to < 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart JANUMET XR if renal function is acceptable (see **PRECAUTIONS**).

IV. DOSAGE FORMS AND STRENGTHS

50 mg/500 mg – Light blue, bi-convex oval, film coated tablet, debossed "78" on one side and plain on the other.
50 mg/1000 mg – Light green, bi-convex oval, film coated tablet, debossed "80" on one side and plain on the other.
100 mg/1000 mg – Blue, bi-convex oval, film coated tablet, debossed "81" on one side and plain on the other.

V. CONTRAINDICATIONS

JANUMET XR (sitagliptin phosphate/metformin HCl extended-release) are contraindicated in patients with:

1. Severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (see **PRECAUTIONS**, *Metformin hydrochloride*, Lactic Acidosis).
2. Known hypersensitivity to sitagliptin phosphate, metformin hydrochloride or any other component of JANUMET XR (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 XR 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*).

VI. PRECAUTIONS

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

Pancreatitis: 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. After initiation of JANUMET XR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUMET XR should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUMET XR.

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. JANUMET XR is contraindicated in severe renal impairment, patients with an eGFR < 30 mL/min/1.73 m^2 (see **DOSAGE AND ADMINISTRATION**, **CONTRAINDICATIONS** and **PRECAUTIONS**, *Metformin hydrochloride*, Lactic acidosis).

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

Hypoglycemia in Combination with a Sulfonylurea or with Insulin: As is typical with other antihyperglycemic agents, hypoglycemia has been observed when sitagliptin and metformin were used in combination with insulin or a sulfonylurea (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 XR. 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 XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. (See **CONTRAINDICATIONS** and **SIDE EFFECTS**, *Postmarketing Experience.*)

Bullous Pemphigoid: Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving JANUMET XR. If bullous pemphigoid is suspected, JANUMET XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Metformin hydrochloride

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET XR (sitagliptin phosphate/metformin HCl extended-release); 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 (see **DOSAGE AND ADMINISTRATION**, *Recommendations for use in renal impairment*). 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 (see **USE IN THE ELDERLY**, *Metformin hydrochloride*). 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 with an eGFR ≥ 30 to < 60 mL/min/1.73 m^2, in patients with a history of hepatic impairment, alcoholism, or heart failure, or in patients who will be administered intra-arterial iodinated contrast, JANUMET XR 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 acceptable (see **DOSAGE AND ADMINISTRATION**).

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 XR therapy, the drug should be promptly discontinued.

Surgical procedures: Use of JANUMET XR 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 acceptable (see **DOSAGE AND ADMINISTRATION**).

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 XR.

Impaired hepatic function: Since impaired hepatic function has been associated with some cases of lactic acidosis, JANUMET XR 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 XR 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 XR 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 XR 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 XR and temporarily administer insulin. JANUMET XR may be reinstituted after the acute episode is resolved.

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

VII. PREGNANCY

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

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

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30 and 20 times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats. Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

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 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

VIII. NURSING MOTHERS

No studies in lactating animals have been conducted with the combined components of JANUMET XR. 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 XR should not be used by a woman who is nursing.

IX. PEDIATRIC USE

The safety and efficacy of the addition of sitagliptin in pediatric patients aged 10 to 17 years with type 2 diabetes and inadequate glycemic control on metformin with or without insulin was assessed in two studies over 54 weeks. The addition of sitagliptin (administered as JANUMET or JANUMET XR) was compared to the addition of placebo to metformin or metformin XR.

The results do not support use of JANUMET or JANUMET XR in pediatric subjects (10 to 17 years old) with type 2 diabetes *[see CLINICAL STUDIES 13]*.

In pediatric patients aged 10 to 17 years with type 2 diabetes, the profile of side effects was comparable to that observed in adults.

JANUMET and JANUMET XR have not been studied in pediatric patients under 10 years of age.

X. USE IN THE ELDERLY

Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, JANUMET XR 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; CLINICAL PHARMACOLOGY.)

Sitagliptin

Of the total number of subjects (N=3884) in Phase II and III clinical studies of sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified

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

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 young patients. The initial and maintenance dosing of metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function. (See **CONTRAINDICATIONS**; **PRECAUTIONS**; and **CLINICAL PHARMACOLOGY.**)

XI. DRUG INTERACTIONS

Sitagliptin and metformin

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

In Vitro Assessment of Drug Interactions

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways.

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

In Vivo Assessment of Drug Interactions

Effect of Sitagliptin on Other Drugs

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

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

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

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

Thiazolidinediones: Single-dose pharmacokinetics of rosiglitazone was not meaningfully altered in subjects receiving multiple daily doses of sitagliptin, indicating that sitagliptin is not an inhibitor of CYP2C8-mediated metabolism.

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

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

Effect of Other Drugs on Sitagliptin

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

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 sitagliptin 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.

Metformin hydrochloride

Glyburide: In a single-dose interaction study in type 2 diabetes patients, coadministration 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 coadministration. 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 coadministered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration 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.

Drugs that reduce metformin clearance: Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

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 XR 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 coadministered 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.

XII. SIDE EFFECTS

Clinical Trials Experience

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

Sitagliptin and Metformin Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise

Table 1 summarizes the most common (≥ 5% of patients) adverse reactions reported (regardless of investigator assessment of causality) in a 24-week placebo-controlled factorial

study in which sitagliptin and metformin were coadministered to patients with type 2 diabetes inadequately controlled on diet and exercise.

Table 1: Sitagliptin and Metformin Coadministered to Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥ 5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)†

	Number of Patients (%)			
	Placebo	Sitagliptin 100 mg once daily	Metformin 500 mg/ Metformin 1000 mg twice daily††	Sitagliptin 50 mg twice daily + Metformin 500 mg/ Metformin 1000 mg twice daily††
	N = 176	N = 179	N = 364††	N = 372††
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)
Upper Respiratory Tract Infection	9 (5.1)	8 (4.5)	19 (5.2)	23 (6.2)
Headache	5 (2.8)	2 (1.1)	14 (3.8)	22 (5.9)

† Intent-to-treat population.

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

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone

In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily metformin regimen, there were no adverse reactions reported regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse reactions was similar to the placebo treatment group (sitagliptin and metformin, 1.9%; placebo and metformin, 2.5%).

Gastrointestinal Adverse Reactions

The incidences of pre-selected gastrointestinal adverse experiences in patients treated with sitagliptin and metformin were similar to those reported for patients treated with metformin alone. See Table 2.

Table 2: Pre-selected Gastrointestinal Adverse Reactions (Regardless of Investigator Assessment of Causality) Reported in Patients with Type 2 Diabetes Receiving Sitagliptin and Metformin						
	Number of Patients (%)					
	Study of Sitagliptin and Metformin in Patients Inadequately Controlled on Diet and Exercise				Study of Sitagliptin Add-on in Patients Inadequately Controlled on Metformin Alone	
	Placebo	Sitagliptin 100 mg once daily	Metformin 500 mg/ Metformin 1000 mg twice daily †	Sitagliptin 50 mg twice daily + Metformin 500 mg/ Metformin 1000 mg twice daily †	Placebo and Metformin ≥ 1500 mg daily	Sitagliptin 100 mg once daily and Metformin ≥ 1500 mg daily
	N = 176	N = 179	N = 364	N = 372	N = 237	N = 464
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 (2.2)	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)

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

† † Abdominal discomfort was included in the analysis of abdominal pain in the study of initial therapy.

Sitagliptin in Combination with Metformin and Glimepiride

In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin and glimepiride (sitagliptin, N=116; placebo, N=113), the adverse reactions reported regardless of investigator assessment of causality in ≥ 5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: hypoglycemia (Table 3) and headache (6.9%, 2.7%).

Sitagliptin in Combination with Metformin and Insulin

In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin and stable-dose insulin (sitagliptin, N=229; placebo, N=233), the only adverse reaction reported regardless of investigator assessment of causality in ≥ 5% of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycemia (Table 3). In another 24-week study of patients receiving sitagliptin as add-on therapy while undergoing insulin intensification (with or without metformin), among patients treated with sitagliptin and metformin, there were no adverse reactions reported regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients treated with placebo and metformin.

Hypoglycemia

In all (N=5) studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required although most (77%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤ 70 mg/dL. When the combination of sitagliptin and metformin was coadministered with a sulfonylurea or with insulin, the percentage of patients reporting at least one adverse reaction of hypoglycemia was higher than that observed with placebo and metformin coadministered with a sulfonylurea or with insulin (Table 3).

Table 3: Incidence and Rate of Hypoglycemia† (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Clinical Studies of Sitagliptin in Combination with Metformin Coadministered with Glimepiride or Insulin

Add-on to Glimepiride + Metformin (24 weeks)	**Sitagliptin 100 mg + Metformin +Glimepiride**	**Placebo + Metformin +Glimepiride**
	N = 116	N = 113
Overall (%)	19 (16.4)	1 (0.9)
Rate (episodes/patient-year)‡	0.82	0.02
Severe (%)§	0 (0.0)	0 (0.0)
Add-On to Insulin + Metformin (24 weeks)	**Sitagliptin 100 mg + Metformin + Insulin**	**Placebo + Metformin + Insulin**
	N = 229	N = 233
Overall (%)	35 (15.3)	19 (8.2)
Rate (episodes/patient-year)‡	0.98	0.61
Severe (%)§	1 (0.4)	1 (0.4)

† Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required: Intent to Treat Population.

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

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

The overall incidence of reported adverse reactions of hypoglycemia in patients with type 2 diabetes inadequately controlled on diet and exercise was 0.6% in patients given placebo, 0.6% in patients given sitagliptin alone, 0.8% in patients given metformin alone, and 1.6% in patients given sitagliptin in combination with metformin. In patients with type 2 diabetes inadequately

controlled on metformin alone, the overall incidence of adverse reactions of hypoglycemia was 1.3% in patients given add-on sitagliptin and 2.1% in patients given add-on placebo.

Vital Signs and Electrocardiograms

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

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 non-adjudicated acute pancreatitis events was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control) (see **PRECAUTIONS**). See also ***TECOS Cardiovascular Safety Study,*** below.

Sitagliptin

The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients given placebo was nasopharyngitis.

Metformin hydrochloride

The most common (>5%) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

TECOS Cardiovascular Safety Study

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline estimated glomerular filtration rate (eGFR) was ≥ 30 and <50 mL/min/1.73 m^2), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA_{1c} and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo. Assessment of pre-specified diabetes-related complications revealed similar incidences between groups including infections (18.4% of the sitagliptin-treated patients and 17.7% of the placebo-treated patients) and renal failure (1.4% of sitagliptin-treated patients and 1.5% of placebo-treated patients). The study population included a total of 2,004 patients ≥ 75 years of age (970 treated with sitagliptin and 1,034 treated with placebo). The adverse event profile in patients ≥ 75 years of age was generally similar to the overall population.

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

Pediatric Population

In a pooled analysis of two placebo-controlled clinical studies with JANUMET and JANUMET XR in pediatric patients aged 10 to 17 years with type 2 diabetes, the drug-related adverse reactions reported through the 54-week treatment period in ≥ 1% of patients in the JANUMET/JANUMET XR group (N=107) and more commonly than in patients in the Metformin/Metformin XR group (N=113) were diarrhea (JANUMET/JANUMET XR, 2.8%; Metformin/Metformin XR, 0.9%), nausea (2.8%, 0.9%), and hypoglycemia (6.5%, 3.5%).

The profile of side effects was comparable to that observed in adults. There were no clinically relevant differences between the JANUMET/JANUMET XR and Metformin/Metformin XR groups through Week 54 in laboratory safety endpoints, vital signs, indices of adiposity, or growth and development endpoints.

Laboratory Tests

Sitagliptin

The incidence of laboratory adverse reactions was similar in patients treated with sitagliptin and metformin (7.6%) compared to patients treated with placebo and metformin (8.7%). In most but not all 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 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**).

Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of sitagliptin with or without metformin, and/or in combination with other antidiabetic medications. 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 **PRECAUTIONS**); upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see

PRECAUTIONS); worsening renal function, including acute renal failure (sometimes requiring dialysis) and tubulointerstitial nephritis; bullous pemphigoid (see PRECAUTIONS, Bullous Pemphigoid); severe and disabling arthralgia (see PRECAUTIONS); constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus.

XIII. 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 (see CLINICAL PHARMACOLOGY, *Pharmacodynamics*, *Cardiac Electrophysiology*). 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.

XIV. AVAILABILITY

JANUMET XR 50 mg/500 mg is available in a bottle of 14 or 56 tablets.
JANUMET XR 50 mg/1000 mg Tablet is available in a bottle of 14 or 56 tablets.
JANUMET XR 100 mg/1000 mg Tablet is available in a bottle of 7 or 28 tablets.

Not all presentations may be available locally.

XV. COMPOSITION

XV a. Active Ingredients

JANUMET XR consists of an extended-release metformin core tablet coated with an immediate release layer of sitagliptin. The sitagliptin layer is coated with a soluble polymeric film that provides taste masking.

JANUMET XR is available for oral administration as tablets containing 64.25 mg sitagliptin phosphate monohydrate (equivalent to 50 mg sitagliptin as free base) and either 500 mg metformin hydrochloride extended-release (JANUMET XR 50 mg/500 mg), or 1000 mg metformin hydrochloride extended-release (JANUMET XR 50 mg/1000 mg). Additionally, JANUMET XR is available for oral administration as tablets containing 128.5 mg sitagliptin phosphate monohydrate (equivalent to 100 mg sitagliptin as free base) and 1000 mg metformin hydrochloride extended-release (100 mg/1000 mg).

XV b. Inactive Ingredients

All doses of JANUMET XR contain the following inactive ingredients: povidone, hypromellose, colloidal silicon dioxide, sodium stearyl fumarate, propyl gallate, polyethylene glycol, and kaolin. The JANUMET XR 50 mg/500 mg tablet contains the additional inactive ingredient microcrystalline cellulose. In addition, the film coating contains the following inactive ingredients: hypromellose, hydroxypropyl cellulose, titanium dioxide, FD&C Blue #2/Indigo Carmine

Aluminum Lake and carnauba wax. The JANUMET XR 50 mg/1000 mg tablet contains the additional inactive ingredient yellow iron oxide.

XVI. STORAGE

Store at or below 30°C.

XVII. CLINICAL PHARMACOLOGY

XVII a. Mechanism of Action

JANUMET XR 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

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

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**]) 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.

XVII b. Pharmacokinetics

The results of a study in healthy subjects demonstrated that the JANUMET XR (sitagliptin/metformin HCl extended-release) 50 mg/500 mg and 100 mg/1000 mg tablets, and coadministration of corresponding doses of sitagliptin (JANUVIA™) and metformin hydrochloride extended-release (GLUMETZA™[1]) as individual tablets are bioequivalent.

Bioequivalence between two JANUMET XR 50 mg/500 mg tablets and one JANUMET XR 100 mg/1000 mg tablet was also demonstrated.

In a crossover study in healthy subjects, the AUC and C_{max} for sitagliptin and AUC for metformin after administration of a single JANUMET XR 50 mg/500 mg tablet probe formulation and administration of a single JANUMET 50 mg/500 mg tablet were similar. After administration of a single JANUMET XR 50 mg/500 mg tablet probe formulation, the mean C_{max} value for metformin was 30% lower and the median T_{max} value occurred 4 hours later compared with corresponding values after administration of a single JANUMET 50 mg/500 mg tablet, which is consistent with the expected modified-release characteristics for metformin associated with the JANUMET XR formulation.

[1] **GLUMETZA** is a trademark of Biovail Laboratories International S.r.l.

After administration of two JANUMET XR 50 mg/1000 mg tablets once daily with the evening meal for 7 days in healthy adult subjects, steady-state for sitagliptin and metformin was reached by Day 4 and 5, respectively. The median T_{max} values for sitagliptin and metformin at steady state were approximately 3 and 8 hours postdose, respectively. The median T_{max} values for sitagliptin and metformin after administration of a single tablet of JANUMET were 3 and 3.5 hours postdose, respectively.

XVII b-1. Absorption

After administration of JANUMET XR tablets with a high-fat breakfast, the AUC for sitagliptin was not altered. The mean C_{max} was decreased by 17%, although the median T_{max} was unchanged relative to the fasted state. After administration of JANUMET XR with a high-fat breakfast, the AUC for metformin increased 62%, the C_{max} for metformin decreased by 9%, and the median T_{max} for metformin occurred 2 hours later relative to the fasted state.

Sitagliptin phosphate

The absolute bioavailability of sitagliptin is approximately 87%. Coadministration of a high-fat meal with sitagliptin phosphate had no effect on the pharmacokinetics of sitagliptin.

Metformin hydrochloride

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alternation in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

XVII b-2. Distribution

Sitagliptin phosphate

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%).

Metformin hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

XVII b-3. Metabolism

Sitagliptin phosphate

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

Metformin hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

XVII b-4. Elimination

Sitagliptin phosphate

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

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

Metformin hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

XVII b-5. Characteristics in Patients

Type 2 Diabetes

Renal Impairment

Sitagliptin phosphate

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to <45 mL/min/1.73 m^2, and an approximately 4-fold increase was observed in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) including patients with end-stage renal disease (ESRD) on hemodialysis, as compared to subjects with normal renal function.

Metformin hydrochloride

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

Hepatic Impairment

Sitagliptin phosphate

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

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

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Gender

Sitagliptin phosphate

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.

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Elderly

Sitagliptin phosphate

When the effects of age on renal function are taken into account, age alone did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see **GLUCOPHAGE**™[2] prescribing information).

Pediatric

[2] **GLUCOPHAGE** is a trademark of Merck Sante S.A.S, an associate of Merck KGaA of Darmstadt, Germany.

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

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

Race

Sitagliptin phosphate

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, Asian, and other racial groups.

Metformin hydrochloride

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

Body Mass Index (BMI)

Sitagliptin phosphate

Body mass index (BMI) 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.

XVII c. Pharmacodynamics

Sitagliptin

General

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

Sitagliptin and Metformin hydrochloride Coadministration

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear what these findings mean for changes in glycemic control in patients with type 2 diabetes. In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.

Cardiac Electrophysiology

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

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

XVII d. Clinical Studies

Clinical studies of the coadministration of sitagliptin and metformin demonstrated significant improvements in glycemic control in adult patients with type 2 diabetes. There have been no clinical efficacy studies in adults conducted with JANUMET or JANUMET XR tablets; however, bioequivalence of JANUMET tablets with coadministered sitagliptin and immediate-release metformin hydrochloride tablets and JANUMET XR tablets with coadministered sitagliptin and extended-release metformin tablets has been demonstrated.

The coadministration of sitagliptin and metformin has been studied in patients with type 2 diabetes inadequately controlled on diet and exercise and in combination with other antihyperglycemic agents.

None of the clinical efficacy studies described below was conducted with JANUMET; however, bioequivalence of JANUMET with coadministered sitagliptin and metformin hydrochloride tablets was demonstrated.

Sitagliptin and Metformin Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise

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

Sitagliptin and metformin coadministration provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to sitagliptin alone (Table 4, Figure 1). Mean reductions from baseline in A1C were generally greater for patients with higher baseline A1C values. For patients not on an antihyperglycemic agent at study entry, mean reductions from baseline in A1C were: sitagliptin 100 mg once daily, -1.1%; metformin 500 mg bid, -1.1%; metformin 1000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin 1000 mg bid, -1.9%; and for patients receiving placebo, -0.2%. Lipid effects were generally neutral. The decrease in body weight in the groups given sitagliptin in combination with metformin was similar to that in the groups given metformin alone or placebo.

Table 4: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise†

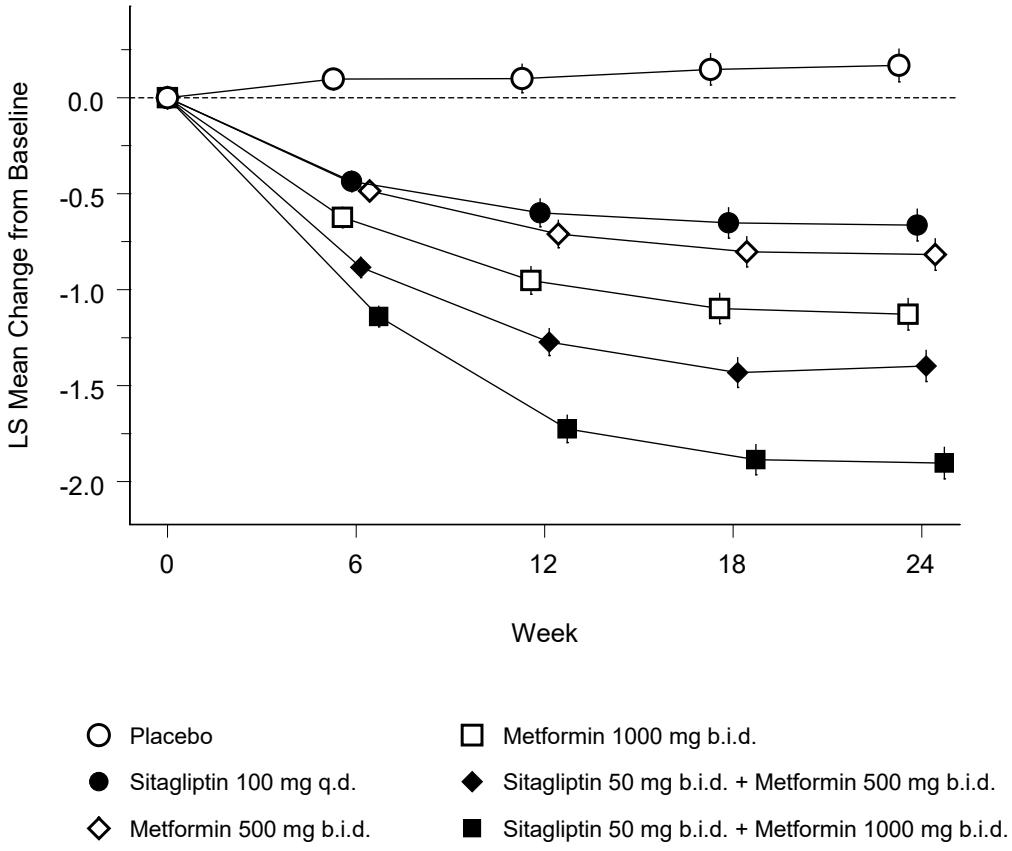
	Placebo	Sitagliptin 100 mg once daily	Metformin 500 mg twice daily	Metformin 1000 mg twice daily	Sitagliptin 50 mg twice daily + Metformin 500 mg twice daily	Sitagliptin 50 mg twice daily + Metformin 1000 mg twice daily
A1C (%)	**N = 165**	**N = 175**	**N = 178**	**N = 177**	**N = 183**	**N = 178**
Baseline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

† Intent to Treat Population using last observation on study prior to glyburide (glibenclamide) rescue therapy.

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

§ p<0.001 compared to placebo.

Figure 1: Mean Change from Baseline for A1C (%) over 24 Weeks with Sitagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled with Diet and Exercise†



† Intention to Treat Population; Least squares means adjusted for prior antihyperglycemic therapy and baseline value.

In addition, this study included patients (N=117) with more severe hyperglycemia (A1C >11% or blood glucose >280 mg/dL) who were treated with twice daily open-label sitagliptin 50 mg and metformin 1000 mg. In this group of patients, the mean baseline A1C value was 11.2%, mean FPG was 314 mg/dL, and mean 2-hour PPG was 441 mg/dL. After 24 weeks, mean decreases from baseline of -2.9% for A1C, -127 mg/dL for FPG, and -208 mg/dL for 2-hour PPG were observed.

Initial combination therapy or maintenance of combination therapy should be individualized and are left to the discretion of the health care provider.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone

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

In combination with metformin, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin (Table 5). Rescue glycemic therapy was used in 5% of patients treated with sitagliptin 100 mg and 14% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table 5: Glycemic Parameters at Final Visit (24-Week Study) of Sitagliptin as Add-on Combination Therapy with Metformin†

	Sitagliptin 100 mg once daily + Metformin	Placebo + Metformin
A1C (%)	**N = 453**	**N = 224**
Baseline (mean)	8.0	8.0
Change from baseline (adjusted mean‡)	-0.7	-0.0
Difference from placebo + metformin (adjusted mean‡) (95% CI)	-0.7§ (-0.8, -0.5)	
Patients (%) achieving A1C <7%	213 (47%)	41 (18%)
FPG (mg/dL)	**N = 454**	**N = 226**
Baseline (mean)	170	174
Change from baseline (adjusted mean‡)	-17	9
Difference from placebo + metformin (adjusted mean‡) (95% CI)	-25§ (-31, -20)	

2-hour PPG (mg/dL)	N = 387	N = 182
Baseline (mean)	275	272
Change from baseline (adjusted mean‡)	-62	-11
Difference from placebo + metformin (adjusted mean‡) (95% CI)	-51§ (-61, -41)	

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

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

§ p<0.001 compared to placebo + metformin.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Glimepiride

A total of 441 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with glimepiride, with or without metformin. Patients entered a run-in treatment period on glimepiride (≥ 4 mg per day) alone or glimepiride in combination with metformin (≥ 1500 mg per day). After a dose-titration and dose-stable run-in period of up to 16 weeks and a 2-week placebo run-in period, patients with inadequate glycemic control (A1C 7.5% to 10.5%) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

Patients receiving sitagliptin with metformin and glimepiride had significant improvements in A1C and FPG compared to patients receiving placebo with metformin and glimepiride (Table 6), with mean reductions from baseline relative to placebo in A1C of -0.9% and in FPG of -21 mg/dL. Rescue therapy was used in 8% of patients treated with add-on sitagliptin 100 mg and 29% of patients treated with add-on placebo. The patients treated with add-on sitagliptin had a mean increase in body weight of 1.1 kg vs. add-on placebo (+0.4 kg vs. -0.7 kg). In addition, add-on sitagliptin resulted in an increased rate of hypoglycemia compared to add-on placebo. (See **PRECAUTIONS**; **SIDE EFFECTS**).

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

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

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

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

§ $p<0.001$ compared to placebo.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Insulin

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin as add-on to stable-dose insulin therapy. Approximately 75% of patients were also taking metformin. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin (≥ 1500 mg per day). Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a pre-mixed insulin. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized to the addition of either 100 mg of sitagliptin (N=229) or placebo (N=233), administered once daily. Patients were on a stable dose of insulin prior to enrollment with no changes in insulin dose permitted during the run-in period. Patients who failed to meet specific glycemic goals during the double-blind treatment period were to have uptitration of the background insulin dose as rescue therapy.

Among patients also receiving metformin, the median daily insulin (pre-mixed, intermediate or long acting) dose at baseline was 40 units in the sitagliptin-treated patients and 42 units in the placebo-treated patients. The median change from baseline in daily dose of insulin was zero for both groups at the end of the study. Patients receiving sitagliptin with metformin and insulin had significant improvements in A1C, FPG and 2-hour PPG compared to patients receiving placebo with metformin and insulin (Table 7). The adjusted mean change from baseline in body weight was -0.3 kg in patients receiving sitagliptin with metformin and insulin and -0.2 kg in patients receiving placebo with metformin and insulin. There was an increased rate of hypoglycemia in patients treated with sitagliptin. (See **PRECAUTIONS**; **SIDE EFFECTS**).

Table 7: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin as Add-on Combination Therapy with Metformin and a stable-dose of Insulin†

	Sitagliptin 100 mg + Metformin + Insulin	**Placebo + Metformin + Insulin**
A1C (%)	**N = 223**	**N = 229**
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean‡ ,§)	-0.7	-0.1
Difference from placebo (adjusted mean‡) 95% CI)	-0.5‖ (-0.7, -0.4)	
Patients (%) achieving A1C <7%	39 (22%)	12 (5%)
FPG (mg/dL)	**N = 225**	**N = 229**
Baseline (mean)	173	176
Change from baseline (adjusted mean‡)	-22	-4
Difference from placebo (adjusted mean‡) (95% CI)	-18‖ (-28, -8.4)	
2-hour PPG (mg/dL)	**N = 182**	**N = 189**
Baseline (mean)	281	281
Change from baseline (adjusted mean‡)	-39	1
Difference from placebo (adjusted mean‡) (95% CI)	-40‖ (-53, -28)	

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

‡ Least squares means adjusted for insulin use at the screening visit, type of insulin used at the screening visit (pre-mixed vs. non pre-mixed [intermediate- or long-acting]), and baseline value.

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

‖ p<0.001 compared to placebo.

In another 24-week, randomized, double-blind, placebo-controlled study designed to assess the insulin-sparing efficacy of sitagliptin as add-on combination therapy, 660 patients with inadequate glycemic control on insulin glargine with or without metformin (≥ 1500 mg per day) were randomized to the addition of either 100 mg of sitagliptin (N=330) or placebo (N=330), administered once daily while undergoing intensification of insulin therapy. Among patients taking metformin, baseline HbA_{1c} was 8.70% and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. Glycemic endpoints measured included HbA_{1c} and FPG.

Among patients taking metformin, at Week 24, the mean increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin (N=285) and 24 IU/day than in patients treated with placebo (N=283). The reduction in HbA_{1c} for patients treated with sitagliptin, metformin, and insulin was -1.35% compared to -0.90% for patients treated with placebo, metformin, and insulin, a difference of -0.45% [95% CI: -0.62, -0.29]. The reduction in FPG for patients treated with sitagliptin, metformin, and insulin was -54.8 mg/dL compared to -43.0 mg/dL for patients treated with placebo, metformin, and insulin, a difference of -11.8 mg/dL [95% CI: -18.7, -4.9]. The incidence of symptomatic hypoglycemia was 24.9% for patients treated with sitagliptin, metformin, and insulin and 37.8% for patients treated with placebo, metformin and insulin. The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycemia (9.1 vs. 19.8%). There was no difference in the incidence of severe hypoglycemia.

Sitagliptin Add-on Therapy vs. Glipizide Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin

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

needed to optimize glycemic control. Thereafter, the glipizide dose was to be kept constant, except for down-titration to prevent hypoglycemia. The mean dose of glipizide after the titration period was 10 mg.

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

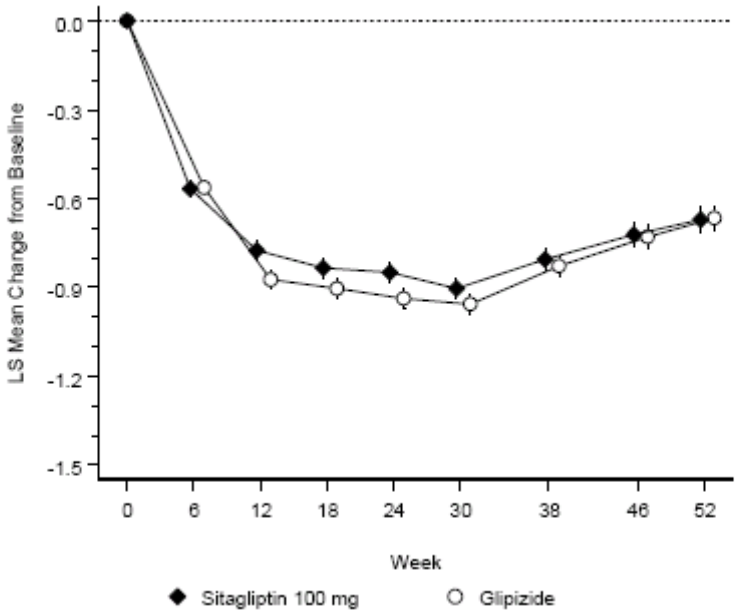
Table 8: Glycemic Parameters in a 52-Week Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin (Intent-to-Treat Population)†

	Sitagliptin 100 mg + Metformin	Glipizide + Metformin
A1C (%)	**N = 576**	**N = 559**
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean‡)	-0.5	-0.6
FPG (mg/dL)	**N = 583**	**N = 568**
Baseline (mean)	166	164
Change from baseline (adjusted mean‡)	-8	-8

† The Intent to Treat Analysis used the patients' last observation in the study prior to discontinuation.

‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline A1C value.

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



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

The incidence of hypoglycemia in the sitagliptin group (4.9%) was significantly ($p<0.001$) lower than that in the glipizide group (32.0%). Patients treated with sitagliptin 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).

TECOS Cardiovascular Safety Study

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a randomized study in 14,671 patients in the intention-to-treat population with an HbA_{1c} of ≥ 6.5 to 8.0% with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and <50 mL/min/1.73 m^2) or placebo (7,339) added to usual care targeting regional standards for HbA_{1c} and CV risk factors. Patients with an eGFR <30 mL/min/1.73 m^2 were not to be enrolled in the study. The study population included 2,004 patients ≥ 75 years of age and 3,324 patients with renal impairment (eGFR <60 mL/min/1.73 m^2).

Over the course of the study, the overall estimated mean (SD) difference in HbA_{1c} between the sitagliptin and placebo groups was 0.29% (0.01), 95% CI (-0.32, -0.27); $p<0.001$. Patients in the

sitagliptin group received fewer antihyperglycemic agents than did those in the placebo group (hazard ratio 0.72; 95% CI, 0.68 to 0.77; p≤ 0.001) and, among patients not on insulin at study entry, were less likely to start chronic insulin therapy (hazard ratio 0.70; 95% CI, 0.63 to 0.79; p<0.001).

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; first occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.

After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalization for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes (Table 9).

Table 9: Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	Sitagliptin 100 mg		Placebo			
	N (%)	Incidence Rate per 100 Patient-Years*	N (%)	Incidence Rate per 100 Patient-Years*	Hazard Ratio (95% CI)	p-value†
Analysis in the Per-Protocol Population						
Number of Patients	**7,257**		**7,266**			
Primary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina)	695 (9.6)	3.7	695 (9.6)	3.8	0.98 (0.88–1.09)	<0.001
Secondary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)	609 (8.4)	3.2	602 (8.3)	3.3	0.99 (0.89–1.11)	<0.001
Analysis in the Intention-to-Treat Population						
Number of Patients	**7,332**		**7,339**		0.98	<0.001

Primary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2	(0.89–1.08)	
Secondary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)	745 (10.2)	3.6	746 (10.2)	3.6	0.99 (0.89–1.10)	<0.001
Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89-1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81–1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79–1.19)	0.760
Hospitalization for unstable angina	116 (1.6)	0.5	129 (1.8)	0.6	0.90 (0.70–1.16)	0.419
Death from any cause	547 (7.5)	2.5	537 (7.3)	2.5	1.01 (0.90–1.14)	0.875
Hospitalization for heart failure‡	228 (3.1)	1.1	229 (3.1)	1.1	1.00 (0.83–1.20)	0.983

* Incidence rate per 100 patient-years is calculated as 100 × (total number of patients with ≥ 1 event during eligible exposure period per total patient-years of follow-up).

† Based on a Cox model stratified by region. For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard ratio is less than 1.3. For all other endpoints, the p-values correspond to a test of differences in hazard rates.

‡ The analysis of hospitalization for heart failure was adjusted for a history of heart failure at baseline.

Sitagliptin Add-on Therapy in Pediatric Patients Inadequately Controlled on Metformin with or without Insulin:

A combined total of 220 pediatric patients aged 10 to 17 years with type 2 diabetes and inadequate glycemic control on metformin with or without insulin participated in two randomized, double-blind, placebo-controlled, parallel-group studies over 54 weeks. The addition of sitagliptin 100 mg (administered as JANUMET or JANUMET XR) was compared to the addition of placebo to metformin or metformin XR.

Superiority of HbA_{1c} reduction was demonstrated for JANUMET/JANUMET XR over metformin at Week 20 in the pooled analysis of these two studies. The reduction in HbA_{1c} in patients treated with JANUMET/JANUMET XR (N=107) was -0.6% compared to -0.1% in patients treated with metformin (N=113), a difference of -0.5% (95% CI: -0.9, -0.1). However, results from the individual studies were inconsistent, and efficacy for JANUMET/JANUMET XR over metformin was not observed at Week 54. These results do not support use of JANUMET or JANUMET XR in pediatric subjects (10 to 17 years old) with type 2 diabetes.

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