PRODUCT MONOGRAPH

PrJANUMET®

sitagliptin and metformin hydrochloride tablets
(as sitagliptin phosphate monohydrate and metformin hydrochloride)

50 mg/500 mg, 50 mg/850 mg and 50 mg/1000 mg

PrJANUMET® XR

sitagliptin and metformin hydrochloride modified-release tablets
(as sitagliptin phosphate monohydrate and metformin hydrochloride)

50 mg/500 mg, 50 mg/1000 mg, 100 mg/1000 mg

Oral Antihyperglycemic Agent
DPP-4 inhibitor
Incretin Enhancer and Biguanide Combination Product

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
oral	tablet 50 mg/500 mg, 50 mg/850 mg, 50 mg/1000 mg modified-release tablet, immediate release sitagliptin (as sitagliptin phosphate monohydrate) / extended-release metformin hydrochloride 50 mg/500 mg, 50 mg/1000 mg, 100 mg/1000 mg	*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

JANUMET® (sitagliptin/metformin) and JANUMET® XR (sitagliptin/metformin HCl modified-release) are indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on metformin or in patients already being treated with the combination of sitagliptin and metformin.

JANUMET® and JANUMET® XR are indicated in combination with a sulfonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on metformin and a sulfonylurea.

JANUMET® and JANUMET® XR are indicated in combination with premixed or long/intermediate acting insulin as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on metformin, and premixed or long/intermediate acting insulin (see CLINICAL TRIALS).

JANUMET® and JANUMET® XR are indicated in combination with pioglitazone in adult patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise, and dual therapy with metformin and pioglitazone do not provide adequate glycemic control.

Geriatrics (≥65 years of age): Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUMET® and 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 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

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

CONTRAINDICATIONS

- Unstable and/or insulin-dependent (Type I) diabetes mellitus.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma. Diabetic ketoacidosis should be treated with insulin.
- In patients with a history of lactic acidosis, irrespective of precipitating factors.
- In the presence of renal impairment or when renal function is not known, and also in patients with serum creatinine levels above the upper limit of normal range. Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥136 μmol/L (males), ≥124 μmol/L (females), or abnormal creatinine clearance (<60 mL/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS AND PRECAUTIONS).
- In excessive alcohol intake, acute or chronic.
- In patients suffering from severe hepatic dysfunction, since severe hepatic dysfunction has been associated with some cases of lactic acidosis, JANUMET® and JANUMET® XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.
- In cases of cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia.
- During stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.
- In patients suffering from severe dehydration.
- Known hypersensitivity to sitagliptin, metformin or to any ingredient in the formulation (see WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions and ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions). For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- During pregnancy and breastfeeding.

JANUMET® and 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 WARNINGS AND PRECAUTIONS, General). JANUMET® and JANUMET® XR should be temporarily discontinued for any surgical procedure necessitating restricted intake of food and fluids and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET® or JANUMET® XR (see Endocrine and Metabolism, Lactic Acidosis section below).
- Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking JANUMET® or JANUMET® XR, since alcohol intake potentiates the effect of metformin on lactate metabolism (see Endocrine and Metabolism, Lactic Acidosis section below).

General

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

Patient Selection and Follow-up
Careful selection of patients is important. It is imperative that there be rigid attention to diet and careful adjustment of dosage. Regular thorough follow-up examinations are necessary.

If vomiting occurs, withdraw drug temporarily, exclude lactic acidosis, then resume dosage cautiously (see ADVERSE REACTIONS).

Particular attention should be paid to short range and long range complications which are peculiar to diabetes. Periodic cardiovascular, ophthalmic, hematological, hepatic and renal assessments are advisable.

Use of JANUMET® or JANUMET® XR must be considered as treatment in addition to proper dietary regimen and not as a substitute for diet.

Care should be taken to ensure that JANUMET® or JANUMET® XR is not given when a contraindication exists.

If during JANUMET® or JANUMET® XR therapy the patient develops acute intercurrent disease such as: clinically significant hepatic dysfunction, cardiovascular collapse, congestive heart failure, acute myocardial infarction, or other conditions complicated by hypoxemia, the drug should be discontinued.

Pancreatitis

There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUMET® or JANUMET® XR. In a long-term cardiovascular outcomes trial (see ADVERSE REACTIONS and CLINICAL TRIALS, TECOS Cardiovascular Safety Study), there were two adjudication-confirmed deaths due to acute pancreatitis in sitagliptin patients compared to none in the placebo group. After initiation of JANUMET® or JANUMET® XR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUMET® or JANUMET® XR should promptly be discontinued and appropriate management should be initiated. Risk factors for pancreatitis include a history of: pancreatitis, gallstones, alcoholism, or hypertriglyceridemia.

Hypoglycemia

When sitagliptin and metformin were used in combination with a sulfonylurea or in combination with insulin; the incidence of hypoglycemia was increased over that of placebo and metformin used in combination with a sulfonylurea or in combination with insulin. To reduce the risk of hypoglycemia associated with these regimens, a lower dose of sulfonylurea or insulin may be considered (see DOSAGE AND ADMINISTRATION).

Hypersensitivity Reactions

There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUMET® and JANUMET® XR. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUMET® or JANUMET® XR, assess for other potential causes for the event, and institute alternative treatment for diabetes (see CONTRAINDICATIONS and ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions).

Cardiovascular

Metformin

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® or JANUMET® XR therapy, the drug should be promptly discontinued.

Endocrine and Metabolism

Metformin

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET® or JANUMET® XR; 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). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. 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 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 and WARNINGS AND PRECAUTIONS, Cardiovascular, Hepatic and Renal).

Physicians should instruct their patients to recognize the symptoms which could be a signal of the onset of lactic acidosis. If acidosis of any kind develops, JANUMET® or JANUMET® XR should be discontinued immediately.

Change in clinical status of previously controlled diabetes patients: A diabetic patient previously well controlled on JANUMET® or 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® or JANUMET® XR must be stopped immediately and 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® or JANUMET® XR and temporarily administer insulin. JANUMET® or JANUMET® XR may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy.

Should secondary failure occur with JANUMET® or JANUMET® XR, therapeutic alternatives should be considered.

Vitamin B_{12} levels: Impairment of vitamin B_{12} absorption has been reported in some patients. Therefore, measurements of serum vitamin B_{12} are advisable at least every one to two years in patients on long-term treatment with JANUMET® or JANUMET® XR.

A decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, is observed in approximately 7% of patients receiving metformin in controlled clinical trials of 29 weeks duration. 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® or JANUMET® XR and any apparent abnormalities should be appropriately investigated and managed (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels.

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.

The patients should be warned about driving a vehicle or operating machinery under these conditions where risk of hypoglycemia is present.

Hepatic

Sitagliptin

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

Metformin

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

Immune

Immunocompromised patients: A dose-related mean decrease in absolute lymphocyte count was observed with other members of this class. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of sitagliptin on lymphocyte counts in patients with lymphocyte abnormalities (e.g. human immunodeficiency virus) is unknown. Immunocompromised patients, such as patients who have undergone organ

transplantation or patients diagnosed with human immunodeficiency syndrome have not been studied in the sitagliptin clinical program. Therefore, the efficacy and safety profile of sitagliptin in these patients has not been established.

Peri-Operative Consideration

Metformin

JANUMET® or JANUMET® XR therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids). JANUMET® or JANUMET® XR should be discontinued 2 days before surgical intervention and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake

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

Renal

Sitagliptin

As metformin is not used in patients with creatinine clearance <60 mL/min, JANUMET® and JANUMET® XR are contraindicated in patients with abnormal creatinine clearance (<60 mL/min) (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; and ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency). Renal adverse events, including acute renal failure, have been observed during clinical trials and post-marketing use of sitagliptin in patients with and without known risk factors (see ADVERSE REACTIONS).

Metformin

Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of the normal range for their age should not receive JANUMET® or JANUMET® XR. In patients with advanced age, JANUMET® and JANUMET® XR should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, renal function should be monitored regularly.

Before initiation of JANUMET® or JANUMET® XR therapy and every 6 months while on JANUMET® or JANUMET® XR therapy, renal function should be assessed and verified as being within normal range.

In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and JANUMET® or JANUMET® XR discontinued if evidence of renal impairment is present.

Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with an NSAID.

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), should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, JANUMET® or 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 normal.

Skin

With other members of this class, ulcerative and necrotic skin lesions have been reported in monkeys in non-clinical toxicology studies. There is limited experience in patients with diabetic skin complications. In keeping with routine care of the diabetic patient, monitoring for skin disorders is recommended.

Bullous Pemphigoid
Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with the use of DPP-4 inhibitor, including JANUMET® or JANUMET® XR. 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® or JANUMET® XR. If bullous pemphigoid is suspected, JANUMET® or JANUMET® XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women with JANUMET® and JANUMET® XR or their individual components; therefore, the safety of JANUMET® and JANUMET® XR in pregnant women is not known. JANUMET® and JANUMET® XR are contraindicated in pregnancy (see also TOXICOLOGY).

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, there is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Women: No studies in lactating animals have been conducted with the combined components of JANUMET® and 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 and/or metformin are excreted in human milk. Therefore, JANUMET® or JANUMET® XR are contraindicated in nursing women.

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

Geriatrics (≥65 years of age):

Sitagliptin and Metformin

Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUMET® or 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 WARNINGS AND PRECAUTIONS, Renal, and DOSAGE AND ADMINISTRATION, Geriatrics).

Sitagliptin

In clinical studies, no overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the geriatric and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin

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

Monitoring and Laboratory Tests

Monitoring of glycemic parameters: Response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA_{1c} levels, with a goal of decreasing these levels towards the normal range. HbA_{1c} is especially useful for evaluating long-term glycemic control.

Monitoring of hematologic parameters: Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

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

Before initiation of therapy with JANUMET® or JANUMET® XR and every 6 months thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and JANUMET® or JANUMET® XR discontinued if evidence of renal impairment is present.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Sitagliptin

Sitagliptin was generally well tolerated in controlled clinical studies as monotherapy and as part of a combination therapy with metformin or combination therapy with metformin and a sulfonylurea or combination therapy with metformin, insulin and pioglitazone.

The incidences of serious adverse reactions and discontinuation of therapy due to clinical adverse reactions were generally similar to placebo. The most frequent adverse events in trials of sitagliptin as monotherapy (placebo-controlled) and as add-on combination therapy with metformin (reported regardless of causality, and more common with sitagliptin than other treatments) was nasopharyngitis. The most frequent adverse reaction with sitagliptin as add-on combination therapy with metformin and a sulfonylurea agent or with metformin and insulin was hypoglycemia.

Metformin

The adverse events most commonly associated with metformin (sitagliptin/metformin) are diarrhea, nausea, and upset stomach. Similar adverse reactions were seen in patients treated with modified-release metformin products. Lactic acidosis is a rare, but serious side effect. Lactic acidosis is fatal in approximately 50% of cases.

Lactic Acidosis: very rare (<1/10, 000 and isolated reports) (see WARNINGS AND PRECAUTIONS, and OVERDOSAGE sections).

Gastrointestinal Reactions: very common: (>1/10) Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to metformin and are approximately 30% more frequent in patients on metformin monotherapy than in placebo-treated patients, particularly during initiation of metformin therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful.

Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take metformin (metformin HCl) with meals (see DOSAGE and ADMINISTRATION).

Because significant diarrhea and/or vomiting can cause dehydration and prerenal azotemia, metformin should be temporarily discontinued, under such circumstances.

For patients who have been stabilized on metformin, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded.

Special Senses: common (≥1/100): During initiation of metformin therapy complaints of taste disturbance are common, i.e. metallic taste.

Dermatologic Reactions: very rare (<1/10,000 and isolated reports): The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for metformin monotherapy and to sulfonylurea for metformin /sulfonylurea therapy. Reports of skin reactions such as erythema, pruritus, and urticaria are very rare.

Hematologic: During controlled clinical trials of 29 weeks duration, approximately 9% of patients on metformin monotherapy and 6% of patients on metformin /sulfonylurea therapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. However, only five cases of megaloblastic anemia have been reported with metformin administration (none during U.S. clinical studies) and no increased incidence of neuropathy has been observed (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin is rare (≥1/10,000 and <1/1,000). Consideration of such aetiology is recommended if a patient presents with megaloblastic anemia.

Hepatic: very rare (<1/10,000 and isolated reports): Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation has been documented in isolated reports.

Clinical Trial Adverse Drug Reactions

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

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

Table 1 – Adverse events ≥1% in any treatment group (regardless of causality) reported in patients in a 24-week placebo-controlled, double-blind clinical trial of sitagliptin in add-on combination use with metformin

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

Table 1 – Adverse events ≥1% in any treatment group (regardless of causality) reported in patients in a 24-week placebo-controlled, double-blind clinical trial of sitagliptin in add-on combination use with metformin

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin n=464**	**Placebo + Metformin n=237**
Contusion	5 (1.1)	1 (0.4)
Investigations		
Blood glucose increased	3 (0.6)	6 (2.5)
Metabolism and nutrition disorders		
Hyperglycemia	2 (0.4)	7 (3.0)
Hypoglycemia	6 (1.3)	5 (2.1)
Musculoskeletal and connective tissue disorders		
Arthralgia	14 (3.0)	1 (0.4)
Back pain	15 (3.2)	6 (2.5)
Muscle spasm	1 (0.2)	3 (1.3)
Myalgia	1 (0.2)	3 (1.3)
Pain in extremity	5 (1.1)	4 (1.7)
Shoulder pain	3 (0.6)	3 (1.3)
Nervous system disorders		
Dizziness	7 (1.5)	2 (0.8)
Headache	12 (2.6)	7 (3.0)
Sciatica	1 (0.2)	3 (1.3)
Sinus headache	0 (0.0)	3 (1.3)
Psychiatric disorders		
Insomnia	5 (1.1)	3 (1.3)
Renal and urinary disorders		
Nephrolithiasis	3 (0.6)	3 (1.3)
Respiratory, thoracic and mediastinal disorders		
Cough	14 (3.0)	4 (1.7)
Vascular disorders		
Hypertension	7 (1.5)	6 (2.5)

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

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

Table 2 – Adverse events ≥1% in any treatment group (regardless of causality) reported in patients from double-blind clinical trials of sitagliptin in add-on combination use with metformin in studies up to one year compared to a sulfonylurea agent (glipizide)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin n=979**	**Glipizide + Metformin n=748**

Table 2 – Adverse events ≥1% in any treatment group (regardless of causality) reported in patients from double-blind clinical trials of sitagliptin in add-on combination use with metformin in studies up to one year compared to a sulfonylurea agent (glipizide)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin n=979**	**Glipizide + Metformin n=748**
Gastrointestinal disorders		
Abdominal pain	10 (1.0)	6 (0.8)
Abdominal pain upper	13 (1.3)	7 (0.9)
Constipation	17 (1.7)	13 (1.7)
Diarrhea	42 (4.3)	36 (4.8)
Dyspepsia	14 (1.4)	12 (1.6)
Nausea	19 (1.9)	16 (2.1)
Toothache	2 (0.2)	13 (1.7)
Vomiting	11 (1.1)	9 (1.2)
General disorders and administration site conditions		
Fatigue	20 (2.0)	8 (1.1)
Non-cardiac chest pain	10 (1.0)	6 (0.8)
Edema peripheral	16 (1.6)	14 (1.9)
Infections and infestations		
Bronchitis	27 (2.8)	22 (2.9)
Cellulitis	7 (0.7)	10 (1.3)
Gastroenteritis	19 (1.9)	13 (1.7)
Gastroenteritis viral	8 (0.8)	9 (1.2)
Herpes zoster	4 (0.4)	8 (1.1)
Influenza	35 (3.6)	32 (4.3)
Nasopharyngitis	75 (7.7)	49 (6.6)
Sinusitis	20 (2.0)	12 (1.6)
Upper respiratory tract infection	78 (8.0)	70 (9.4)
Urinary tract infection	41 (4.2)	21 (2.8)
Investigations		
Blood glucose decreased	5 (0.5)	16 (2.1)
Blood glucose increased	13 (1.3)	5 (0.7)
Weight increased	1 (0.1)	8 (1.1)
Metabolism and nutrition disorders		
Hyperglycemia	10 (1.0)	6 (0.8)
Hypoglycemia	32 (3.3)	217 (29.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	34 (3.5)	29 (3.9)
Back pain	39 (4.0)	32 (4.3)
Muscle spasms	9 (0.9)	8 (1.1)
Neck pain	4 (0.4)	8 (1.1)
Osteoarthritis	18 (1.8)	5 (0.7)
Pain in extremity	23 (2.3)	9 (1.2)
Shoulder pain	7 (0.7)	14 (1.9)
Nervous system disorders		
Dizziness	26 (2.7)	14 (1.9)
Headache	34 (3.5)	31 (4.1)
Hypoaesthesia	3 (0.3)	11 (1.5)

Table 2 – Adverse events ≥1% in any treatment group (regardless of causality) reported in patients from double-blind clinical trials of sitagliptin in add-on combination use with metformin in studies up to one year compared to a sulfonylurea agent (glipizide)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin n=979**	**Glipizide + Metformin n=748**
Psychiatric disorders		
Anxiety	13 (1.3)	7 (0.9)
Depression	10 (1.0)	7 (0.9)
Insomnia	12 (1.2)	11 (1.5)
Reproductive system and breast disorders		
Erectile dysfunction	6 (0.6)	8 (1.1)
Respiratory, thoracic and mediastinal disorders		
Cough	19 (1.9)	23 (3.1)
Pharyngolaryngeal pain	10 (1.0)	9 (1.2)
Sinus congestion	5 (0.5)	8 (1.1)
Eczema	4 (0.4)	12 (1.6)
Vascular disorders		
Hypertension	33 (3.4)	29 (3.9)

Combination Therapy: Sitagliptin add-on to Metformin and a Sulfonylurea

In a 24-week placebo-controlled study of sitagliptin 100 mg in combination with metformin and glimepiride (sitagliptin, N=116; placebo, N=113), the incidence of adverse events, reported regardless of causality assessment, in ≥1% of patients are shown in Table 3. The overall incidence of adverse events with sitagliptin was higher than with placebo, in part related to higher incidence of hypoglycemia (see Table 3).

Table 3 – Adverse events ≥1% in any treatment group (regardless of causality) reported in patients in a 24-week placebo-controlled, double-blind clinical trial of JANUVIA® in add-on combination use with metformin and a sulfonylurea agent (glimepiride)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Glimepiride n=116**	**Placebo + Metformin + Glimepiride n=113**
Ear and Labyrinth Disorders		
Vertigo	2 (1.7)	0 (0.0)
Eye Disorders		
Diabetic retinopathy	0 (0.0)	2 (1.8)
Vision blurred	0 (0.0)	2 (1.8)
Gastrointestinal disorders		
Abdominal pain upper	2 (1.7)	2 (1.8)
Constipation	4 (3.4)	0 (0.0)
Diarrhea	1 (0.9)	4 (3.5)
Dyspepsia	3 (2.6)	2 (1.8)
Gastritis	0 (0.0)	4 (3.5)
Toothache	2 (1.7)	2 (1.8)
Vomiting	2 (1.7)	1 (0.9)

Table 3 – Adverse events ≥1% in any treatment group (regardless of causality) reported in patients in a 24-week placebo-controlled, double-blind clinical trial of JANUVIA® in add-on combination use with metformin and a sulfonylurea agent (glimepiride)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Glimepiride n=116**	**Placebo + Metformin + Glimepiride n=113**
General disorders and administration site conditions		
Fatigue	0 (0.0)	3 (2.7)
Non-Cardiac chest pain	2 (1.7)	1 (0.9)
Pyrexia	0 (0.0)	2 (1.8)
Hepatobiliary disorders		
Cholelithiasis	0 (0.0)	2 (1.8)
Infections and infestations		
Bronchitis	2 (1.7)	2 (1.8)
Gastroenteritis	3 (2.6)	0 (0.0)
Gastroenteritis viral	2 (1.7)	2 (1.8)
Influenza	3 (2.6)	2 (1.8)
Nasopharyngitis	7 (6.0)	9 (8.0)
Pharyngitis	1 (0.9)	3 (2.7)
Pneumonia	3 (2.6)	0 (0.0)
Rhinitis	2 (1.7)	0 (0.0)
Sinusitis	1 (0.9)	2 (1.8)
Tooth abscess	2 (1.7)	1 (0.9)
Upper respiratory tract infection	8 (6.9)	9 (8.0)
Urinary tract infection	2 (1.7)	1 (0.9)
Injury, poisoning and procedural complications		
Fall	0 (0.0)	3 (2.7)
Polytraumatism	1 (0.9)	2 (1.8)
Investigations		
Blood glucose decreased	0 (0.0)	2 (1.8)
Metabolism and nutrition disorders		
Hypoglycemia	19 (16.4)	1 (0.9)
Musculoskeletal and connective tissue disorders		
Arthralgia	5 (4.3)	1 (0.9)
Back pain	1 (0.9)	2 (1.8)
Muscle spasms	2 (1.7)	1 (0.9)
Osteoarthritis	2 (1.7)	0 (0.0)
Pain in extremity	4 (3.4)	1 (0.9)
Shoulder pain	0 (0.0)	2 (1.8)
Nervous system disorders		
Dizziness	3 (2.6)	1 (0.9)
Headache	8 (6.9)	3 (2.7)
Hypoaesthesia	2 (1.7)	0 (0.0)
Somnolence	0 (0.0)	2 (1.8)
Respiratory, thoracic and mediastinal disorders		
Asthma	2 (1.7)	1 (0.9)

Table 3 – Adverse events ≥1% in any treatment group (regardless of causality) reported in patients in a 24-week placebo-controlled, double-blind clinical trial of JANUVIA® in add-on combination use with metformin and a sulfonylurea agent (glimepiride)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Glimepiride n=116**	**Placebo + Metformin + Glimepiride n=113**
Skin and subcutaneous tissue disorders		
Pruritus	2 (1.7)	1 (0.9)
Rash	2 (1.7)	1 (0.9)
Vascular disorders		
Hypertension	2 (1.7)	0 (0.0)

In a combination therapy study with metformin and a sulfonylurea, hypoglycemia (sitagliptin 13.8%; placebo 0.9%) and constipation (sitagliptin 1.7%; placebo 0.0%) were the only drug-related adverse reactions reported by the investigator that occurred with an incidence ≥1% in patients receiving sitagliptin and metformin and a sulfonylurea and greater than in patients receiving placebo and metformin and a sulfonylurea.

Combination Therapy: Add-on with Insulin (with or without metformin)

In a 24-week placebo-controlled study of sitagliptin 100 mg once daily added to ongoing combination treatment with metformin and insulin (sitagliptin, N=229; placebo, N=233), the only adverse experience reported regardless of causality assessment in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycemia (sitagliptin, 15.3%; placebo, 8.2%).

Table 4 – Adverse events ≥1% in any treatment group (regardless of causality) reported in patients in a 24-week placebo-controlled, double-blind clinical trial of sitagliptin in add-on combination use with metformin and insulin

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Insulin n=229**	**Placebo + Metformin + Insulin n=233**
Gastrointestinal Disorders		
Constipation	4 (1.7)	0 (0.0)
Diarrhea	4 (1.7)	4 (1.7)
Nausea	2 (0.9)	4 (1.7)
Vomiting	4 (1.7)	2 (0.9)
General disorders and administration site conditions		
Asthenia	3 (1.3)	1 (0.4)
Fatigue	0 (0.0)	3 (1.3)
Infections and infestations		
Bronchitis	5 (2.2)	4 (1.7)
Gastroenteritis	1 (0.4)	3 (1.3)
Influenza	9 (3.9)	9 (3.9)
Nasopharyngitis	7 (3.1)	7 (3.0)
Respiratory tract infection	3 (1.3)	2 (0.9)
Sinusitis	2 (0.9)	4 (1.7)
Upper respiratory tract infection	8 (3.5)	10 (4.3)
Urinary tract infection	5 (2.2)	5 (2.1)
Viral infection	0 (0.0)	3 (1.3)
Investigations		
Creatinine renal clearance decreased	3 (1.3)	0 (0.0)
Metabolism and nutrition disorders		
Hypoglycemia	35 (15.3)	19 (8.2)
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (0.4)	5 (2.1)
Muscle spasms	0 (0.0)	4 (1.7)
Musculoskeletal pain	2 (0.9)	3 (1.3)
Pain in extremity	4 (1.7)	2 (0.9)
Nervous system disorders		
Dizziness	2 (0.9)	3 (1.3)
Headache	3 (1.3)	2 (0.9)
Respiratory, thoracic and mediastinal disorders		
Cough	2 (0.9)	3 (1.3)

Combination Therapy: Sitagliptin add-on to Metformin and Pioglitazone

In a 26-week placebo-controlled clinical study of patients receiving sitagliptin (100 mg daily) as add-on combination therapy with metformin and pioglitazone, the incidence of adverse events reported regardless of causality assessment, in ≥1% of patients are shown in Table 5.

Table 5 – Adverse events ≥1% in any treatment group (regardless of causality) reported in patients in a 26-week placebo-controlled, double-blind clinical trial of JANUVIA® in add-on combination use with metformin and pioglitazone

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Pioglitazone n=157**	**Placebo + Metformin + Pioglitazone n=156**
Ear and Labyrinth Disorders		
Cerumen impaction	2 (1.3)	1 (0.6)
Eye Disorders		
Conjunctivitis	3 (1.9)	1 (0.6)
Ocular hyperaemia	0 (0.0)	2 (1.3)
Gastrointestinal disorders		
Abdominal pain upper	1 (0.6)	2 (1.3)
Constipation	2 (1.3)	1 (0.6)
Dental Caries	2 (1.3)	1 (0.6)
Diarrhea	3 (1.9)	4 (2.6)
Dyspepsia	1 (0.6)	2 (1.3)
Gastritis	0 (0.0)	2 (1.3)
Toothache	2 (1.3)	0 (0.0)
Vomiting	2 (1.3)	0 (0.0)
General disorders and administration site conditions		
Fatigue	0 (0.0)	2 (1.3)
Oedema peripheral	3 (1.9)	7 (4.5)
Infections and infestations		
Bronchitis	3 (1.9)	1 (0.6)
Cellulitis	2 (1.3)	0 (0.0)
Gastroenteritis	2 (1.3)	0 (0.0)
Gastroenteritis viral	2 (1.3)	0 (0.0)
Herpes zoster	2 (1.3)	0 (0.0)
Influenza	2 (1.3)	3 (1.9)
Nasopharyngitis	5 (3.2)	5 (3.2)
Tooth abscess	0 (0.0)	2 (1.3)
Upper respiratory tract infection	13 (8.3)	14 (9.0)
Urinary tract infection	5 (3.2)	6 (3.8)
Injury, poisoning and procedural complications		
Muscle strain	2 (1.3)	0 (0.0)
Investigations		
Blood creatine phosphokinase increased	1 (0.6)	3 (1.9)
Glomerular filtration rate decreased	2 (1.3)	0 (0.0)
Lymphocyte count increased	2 (1.3)	1 (0.6)
Neutrophil count decreased	2 (1.3)	1 (0.6)
Metabolism and nutrition disorders		
Hyperglycemia	2 (1.3)	2 (1.3)
Hypoglycemia	10 (6.4)	7 (4.5)
Musculoskeletal and connective tissue disorders		
Arthralgia	2 (1.3)	3 (1.9)
Back pain	7 (4.5)	4 (2.6)

Table 5 – Adverse events ≥1% in any treatment group (regardless of causality) reported in patients in a 26-week placebo-controlled, double-blind clinical trial of JANUVIA® in add-on combination use with metformin and pioglitazone

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Pioglitazone n=157**	**Placebo + Metformin + Pioglitazone n=156**
Muscle spasms	2 (1.3)	0 (0.0)
Musculoskeletal pain	3 (1.9)	4 (2.6)
Pain in extremity	5 (3.2)	2 (1.3)
Nervous system disorders		
Headache	1 (0.6)	2 (1.3)
Psychiatric disorders		
Depression	4 (2.5)	1 (0.6)
Stress	2 (1.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
Cough	2 (1.3)	2 (1.3)
Oropharyngeal pain	2 (1.3)	0 (0.0)
Rhinitis allergic	2 (1.3)	0 (0.0)

In a combination therapy study with metformin and pioglitazone, hypoglycemia (JANUVIA®, 3.2%; placebo, 1.9%), was the only drug-related adverse reaction reported by the investigator that occurred with an incidence ≥1% in patients receiving JANUVIA® and greater than in patients receiving placebo.

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

Cardiac Disorders: bundle branch block
Eye Disorders: vision blurred
Gastrointestinal Disorders: abdominal discomfort, abdominal pain upper, constipation, diarrhea, dry mouth, dyspepsia, flatulence, irritable bowel syndrome, reflux esophagitis disease, retching
General Disorders and Administration Site Conditions: asthenia, face edema, hunger, irritability, malaise, peripheral edema, pain
Hepatobiliary Disorders: hepatic steatosis
Infections and Infestations: gastric ulcer helicobacter, helicobacter gastritis, localized infection, oropharyngeal candidiasis, upper respiratory tract infection, urinary tract infection
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose decreased, creatinine renal clearance decreased, glomerular filtration rate decreased, white blood cell count increased
Metabolism and Nutrition Disorders: decreased appetite, hypoglycemia
Musculoskeletal and Connective Tissue Disorders: muscle tightness, muscle fatigue
Nervous System Disorders: dizziness, headache, migraine, neuropathy peripheral, parosmia, somnolence
Psychiatric Disorders: insomnia
Reproductive System and Breast Disorders: dysmenorrhea, erectile dysfunction
Respiratory, Thoracic and Mediastinal Disorders: cough

Skin and Subcutaneous Tissue Disorders: dermatitis acneiform, dry skin, exanthem, rash, urticaria
Vascular Disorders: orthostatic hypotension

Atrial fibrillation/atrial flutter: In a pooled analysis of randomized clinical trials, the pooled terms atrial fibrillation/atrial flutter were observed at an incidence rate of 0.45 events per 100 patient-years in the sitagliptin-exposed group compared to 0.28 events per 100 patient-years in the non-exposed group.

TECOS Cardiovascular Safety Study:
For details pertaining to study design and patient population, see CLINICAL TRIALS, TECOS Cardiovascular Safety Study.

The incidence of adjudication-confirmed pancreatitis events was higher in the sitagliptin group (0.3%) compared to the placebo group (0.2%). The sitagliptin group experienced a greater number of severe cases of pancreatitis including two confirmed deaths due to pancreatitis, compared to none in the placebo group.
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.

Abnormal Hematologic and Clinical Chemistry Findings

Sitagliptin

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

Mean Change from Baseline (Standard Error)				
Study	**Treatment Group**	**Alkaline Phosphatase (IU/L)**	**Uric Acid (mg/dL)**	**WBC (cell/microl)**
Placebo-controlled[1]	Sitagliptin	-3.1 (0.4)	0.17 (0.04)	346.0 (64.3)
	Placebo	-1.3 (0.7)	0.05 (0.06)	142.4 (98.8)
Active-controlled[2]	Sitagliptin	-5.7 (0.5)	0.21 (0.05)	207.8 (67.4)
	Glipizide	-3.4 (0.5)	0.20 (0.05)	86.0 (62.5)

[1] Sitagliptin in Combination with Metformin – Placebo-Controlled Study, see CLINICAL TRIALS
[2] Sitagliptin in Combination with Metformin – Active-Controlled (Sulfonylurea Agent) Study, see CLINICAL TRIALS

In a combination therapy study with insulin and metformin, a greater proportion of patients were observed to have a decrease in hemoglobin ≥1.5 g/dL in the sitagliptin group (6.8%) compared with the placebo group (2.3%).

Metformin

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 WARNINGS AND PRECAUTIONS).

Post-Marketing Adverse Drug Reactions

The following adverse reactions have been identified during post-marketing use of JANUMET® or JANUMET® XR or sitagliptin, used alone and/or in combination with other antihyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis and exfoliative skin conditions, including Stevens-Johnson syndrome (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions);
Renal and urinary disorders: worsening renal function, including acute renal failure (sometimes requiring dialysis) (see WARNINGS AND PRECAUTIONS)
Gastrointestinal disorders: acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see WARNINGS AND PRECAUTIONS); constipation; vomiting
Musculoskeletal and connective tissue disorders: arthralgia; myalgia; pain in extremity; back pain
Nervous system disorders: headache
Skin and subcutaneous tissue disorder: pruritus, bullous pemphigoid (see WARNINGS AND PRECAUTIONS, Skin)

DRUG INTERACTIONS

Overview

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® or JANUMET® XR have not been performed; however, such studies have been conducted with sitagliptin and metformin.

Sitagliptin

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.

Metformin

The simultaneous administration JANUMET® and JANUMET® XR and a sulfonylurea could produce a hypoglycemic reaction, especially if they are given in patients already receiving other drugs which, themselves, can potentiate the effect of sulfonylureas. These drugs can be: long-acting sulfonamides, tubercolostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid and propanolol.

In healthy volunteers, the pharmacokinetics of propranolol and ibuprofen were not affected by metformin 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.

Drug-Drug Interactions

Sitagliptin

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

Metformin: Coadministration of multiple twice-daily doses of sitagliptin with metformin, an OCT substrate, did not meaningfully alter the pharmacokinetics of metformin or sitagliptin in patients with type 2 diabetes. Therefore, sitagliptin is not an inhibitor of OCT-mediated transport.

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

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

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

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

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

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

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

Metformin

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.

Cationic drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JANUMET®, JANUMET® XR and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, isoniazid and beta-2-agonists. ACE-inhibitors may decrease the blood glucose levels. When such drugs are administered to a patient receiving JANUMET® or JANUMET® XR the patient should be closely observed to maintain adequate glycemic control.

Elimination rate of the anticoagulant phenprocoumon has been reported to be increased by 20% when used concurrently with metformin. Therefore, patients receiving phenprocoumon or other antivitamin K anticoagulants should be monitored carefully when both types of drugs are used simultaneously. In such cases, an important increase of prothrombin time may occur upon cessation of JANUMET® or JANUMET® XR therapy, with an increased risk of hemorrhage.

Drug-Food Interactions

There are no known interactions with food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

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 and WARNINGS AND PRECAUTIONS).

Drug-Lifestyle Interactions

Sitagliptin and Metformin

No studies of the effects of JANUMET® or JANUMET® XR on the ability to drive and use machines have been performed. JANUMET® and JANUMET® XR are not expected to affect the ability to drive and use machines under usual circumstances. However, patients should be warned about driving a vehicle or operating machinery under conditions where a risk of hypoglycemia is present (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Metformin). When JANUMET® or JANUMET® XR is used in combination with a sulfonylurea or in combination with insulin patients should be advised to take precautions to avoid hypoglycaemia while driving or using machinery.

Metformin

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking JANUMET® or JANUMET® XR, since alcohol intake potentiates the effect of metformin on lactate metabolism (see CONTRAINDICATIONS).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Over a period of time, patients may become progressively less responsive to therapy with oral hypoglycemic agents because of deterioration of their diabetic state. Patients should therefore be monitored with regular clinical and laboratory evaluations, including blood glucose and glycosylated hemoglobin (A_{1c}) determinations, to determine the minimum effective dosage and to detect primary failure or secondary failure (see WARNINGS AND PRECAUTIONS).

In patients in whom the maximum dose fails to lower the blood glucose adequately, therapeutic alternatives should be considered.

The dosage of antihyperglycemic therapy with JANUMET® or 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® should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects associated to 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 very rare reports of incompletely dissolved JANUMET® XR tablets being eliminated in the feces. If a patient reports seeing tablets in feces, the healthcare provider should assess adequacy of glycemic control. If glycemic control is found to be reduced, alternative treatments should be considered. (see CONSUMER INFORMATION.)

Recommended Dose and Dosage Adjustment

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

JANUMET® should be given twice daily with meals. JANUMET® tablets are available in the following strengths:

50 mg sitagliptin/500 mg metformin hydrochloride
50 mg sitagliptin/850 mg metformin hydrochloride
50 mg sitagliptin/1000 mg metformin hydrochloride

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 metformin hydrochloride modified release tablet
50 mg sitagliptin/1000 mg metformin hydrochloride modified release tablet
100 mg sitagliptin/1000 mg metformin hydrochloride modified release tablet

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

No studies have been performed specifically examining the safety and efficacy of JANUMET® or JANUMET® XR in patients previously treated with other oral antihyperglycemic agents and switched to JANUMET® or 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.

Patients inadequately controlled on metformin monotherapy: For patients inadequately controlled on metformin alone, the recommended total daily starting dose of JANUMET® or JANUMET® XR is 100 mg sitagliptin and the previously prescribed dose of metformin.

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

Patients inadequately controlled on dual combination therapy with metformin and a sulfonylurea: The dose of JANUMET® or JANUMET® XR should provide 100 mg total daily dose of sitagliptin and a dose of metformin similar to the dose already being taken. When JANUMET® or JANUMET® XR are used in combination with a sulfonylurea a lower dose of the sulfonylurea may be required to reduce the risk of hypoglycemia (see WARNINGS AND PRECAUTIONS, Hypoglycemia).

Patients inadequately controlled on dual combination therapy with any two of the following three antihyperglycemic agents: sitagliptin, metformin and insulin: The dose of JANUMET® or 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 CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Patients inadequately controlled on dual combination therapy with metformin and pioglitazone: The usual starting dose of JANUMET® or JANUMET® XR should provide 100 mg total daily dose of sitagliptin plus the dose of metformin already being taken.

Patients with Renal Insufficiency: JANUMET® or JANUMET® XR should not be used in patients with renal failure or renal dysfunction e.g., serum creatinine levels ≥136 μmol/L (males), ≥124 μmol/L (females) or abnormal creatinine clearance (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Patients with Hepatic Insufficiency: Use of JANUMET® or JANUMET® XR in patients with severe hepatic insufficiency is not recommended (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Geriatrics: As metformin and sitagliptin are excreted by the kidney, JANUMET® or JANUMET® XR should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Lactic Acidosis and ACTION AND CLINICAL PHARMACOLOGY, Geriatrics).

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

Missed Dose

If a dose of JANUMET® or JANUMET® XR is missed, it should be taken as soon as the patient remembers. If he/she does not remember until it is time for the next dose, the missed dose should be skipped and returned to the regular schedule. Two doses of JANUMET® or JANUMET® XR (see DOSAGE AND ADMINISTRATION) should not be taken at the same time.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Sitagliptin

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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). There is no experience with doses above 800 mg in clinical trials. 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 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

Available information concerning treatment of a massive overdosage of metformin hydrochloride is very limited. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded. The drug should be discontinued and proper supportive therapy instituted.

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 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Lactic Acidosis). 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

JANUMET® and JANUMET® XR

JANUMET® and 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. JANUMET® and JANUMET® XR targets three core defects of type 2 diabetes which are: decreased insulin synthesis and release, increased hepatic glucose production and decreased insulin sensitivity.

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

Sitagliptin

Sitagliptin 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 enhancer.

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. 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. Orally administered glucose provokes a higher insulin response than that of intravenously administered glucose by raising circulating incretin levels (the incretin effect). In patients with type 2 diabetes, the incretin effect is diminished. Progressive beta-cell failure is a feature characterizing the pathogenesis of type 2 diabetes. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced.

In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose dependent such that when blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin release is enhanced as glucose rises above normal concentrations. Further, GLP-1 does not impair the normal glucagon response to hypoglycemia.

The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner.

In patients with type 2 diabetes with hyperglycemia, these changes in insulin and glucagon levels lead to lower hemoglobin A_{1c} (HbA_{1c}) and lower fasting and postprandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulfonylureas, which increase insulin secretion even when glucose levels are low, which can lead to 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. Inhibition of DPP-8 or DPP-9, but not DPP-4, is associated with toxicity in preclinical animal models and alteration of immune function *in vitro*.

Metformin

Metformin is an antihyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin is a biguanide derivative producing an antihyperglycemic effect which is observed in diabetic patients or in diabetic animals. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin may decrease hepatic glucose production, decrease intestinal absorption of glucose, and improve 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 WARNINGS AND PRECAUTIONS, Hypoglycemia) 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.

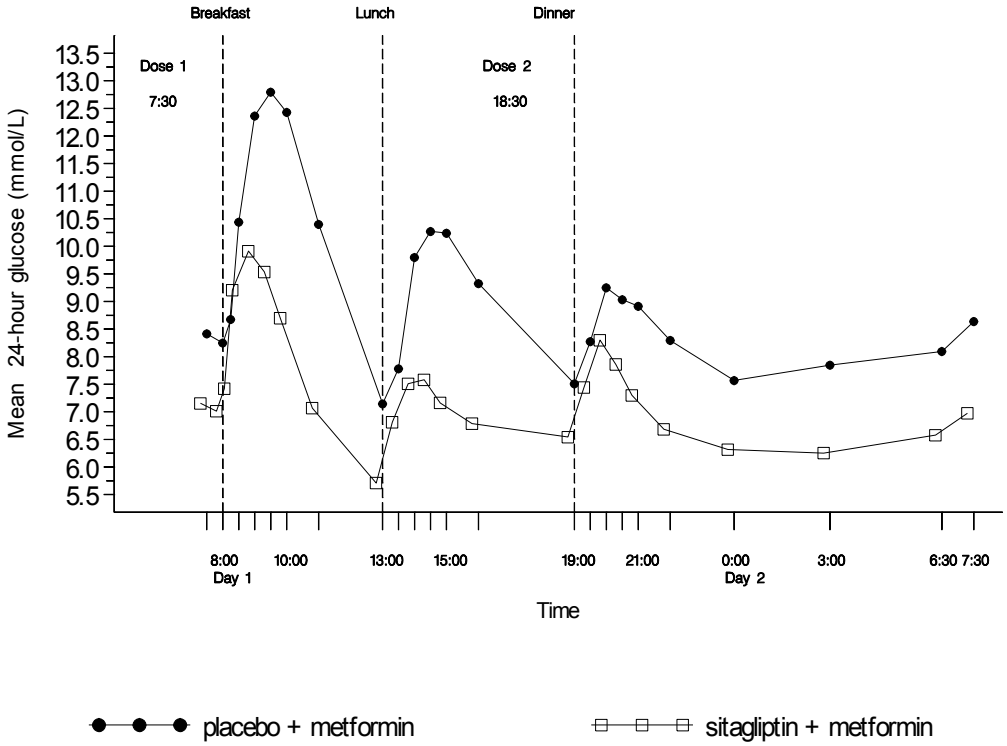
Pharmacodynamics

Sitagliptin

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

In a study of patients with type 2 diabetes inadequately controlled on metformin monotherapy (N=26), glucose levels monitored throughout the day were significantly lower ($p<0.001$) in patients who received sitagliptin 100 mg per day (50 mg twice daily) in combination with metformin compared with patients who received placebo with metformin (see Figure 1).

Figure 1 – 24-hour plasma glucose profile after 4-week treatment with sitagliptin 50 mg BID with metformin or placebo with metformin



Sitagliptin and Metformin 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 has 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 patient with type 2 diabetes.

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

Cardiac Electrophysiology: In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of 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 (90% CI 5.5, 10.6). At the 800-mg dose, peak sitagliptin plasma concentrations were approximately 11-time 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.

Pharmacokinetics

JANUMET®

In a bioequivalence study of JANUMET® 50/500 and 50/1000 (mg/mg sitagliptin/metformin hydrochloride), both the sitagliptin component and the metformin component were bioequivalent to coadministered 50 mg sitagliptin phosphate (JANUVIA®) tablet and metformin hydrochloride tablets 500 and 1000 mg, respectively under fasted conditions in healthy subjects.

Because bioequivalence is demonstrated at the lowest and highest combination tablet dose strengths available, bioequivalence is conferred to the (sitagliptin/metformin) 50 mg/850 mg fixed dose combination (FDC) tablet.

Table 6 – Geometric Mean Pharmacokinetic Parameters for Sitagliptin and Metformin Following Single Dose of JANUMET® or Coadministration of Corresponding Doses of Sitagliptin and Metformin as Individual Tablets to Healthy Subjects Under Fasted Conditions

Sitagliptin					
Treatment	**Subject Number**	**$AUC_{0-\infty}$ (µM·hr)**	**C_{max} (nM)**	**T_{max}† (hr)**	**$t_{1/2}$‡ (hr)**
A	24	4.09	415	2.50	12.3
B	24	4.01	414	2.75	12.6
C	24	4.05	423	2.50	13.1
D	24	3.94	397	2.50	13.7
Metformin					
Treatment	**Subject Number**	**$AUC_{0-\infty}$ (µg/mL·hr)**	**C_{max} (ng/mL)**	**T_{max}† (hr)**	**$t_{1/2}$‡ (hr)**
A	24	7.26	1180	2.50	9.79
B	24	7.25	1180	2.75	11.6
C	24	11.9	1850	2.50	13.6
D	24	11.9	1870	2.00	13.9

† Median
‡ Harmonic Mean
Treatment A = sitagliptin 50 mg + metformin hydrochloride 500 mg
Treatment B = JANUMET® sitagliptin (50 mg)/metformin hydrochloride (500 mg)
Treatment C = sitagliptin 50 mg + metformin hydrochloride 1000 mg
Treatment D = JANUMET® sitagliptin (50 mg)/metformin hydrochloride (1000 mg)

When administered in the fed state (following a standard high-fat breakfast), the metformin component of JANUMET® was bioequivalent to metformin taken together with sitagliptin as individual tablets.

JANUMET® XR

The results of studies in healthy subjects demonstrated that the JANUMET® XR 50 mg/500 mg and 100 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding individual doses of sitagliptin (JANUVIA®) tablets and metformin hydrochloride extended-release (GLUMETZA*) tablets.

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 50 mg/1000 mg tablet of JANUMET® were 3 and 3.5 hours postdose, respectively.

Absorption:

Sitagliptin

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

Metformin

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 immediate-release 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 alteration 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.

Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from 500 mg GLUMETZA* tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected.

Distribution:

Sitagliptin

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

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 μg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 μg/mL, even at maximum doses.

Metabolism:

Sitagliptin

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

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.

Excretion:

Sitagliptin

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

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.

Special Populations and Conditions

Pediatrics: No studies with JANUMET® or JANUMET® XR have been performed in pediatric patients.

Geriatrics:

Sitagliptin

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

Metformin

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 WARNINGS AND PRECAUTIONS, Geriatrics).

JANUMET® or JANUMET® XR treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Lactic Acidosis).

Gender: No dosage adjustment is necessary based on gender.

Sitagliptin

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

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.

Race: No dosage adjustment is necessary based on race.

Sitagliptin

Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic

analysis of Phase I and Phase II data, including subjects of white, Hispanic, black and Asian racial groups.

Metformin

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).

Hepatic Insufficiency:

Sitagliptin

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

Metformin

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

Renal Insufficiency:

JANUMET® or JANUMET® XR should not be used in patients with renal insufficiency (see CONTRAINDICATIONS).

Sitagliptin

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

Metformin

In patients with decreased renal function (based on measured creatinine clearance (<60 mL/min), the plasma and blood half-lifes of metformin are prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

STORAGE AND STABILITY

JANUMET® and JANUMET® XR

The product should be stored at 15 °C–30 °C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

JANUMET®
Tablets JANUMET®, 50 mg/500 mg, are light pink, capsule-shaped, film-coated tablets with "575" debossed on one side. They are supplied in bottles of 60.

Tablets JANUMET®, 50 mg/850 mg, are pink, capsule-shaped, film-coated tablets with "515" debossed on one side. They are supplied in bottles of 60.

Tablets JANUMET®, 50 mg/1000 mg, are red, capsule-shaped, film coated tablets with "577" debossed on one side. They are supplied in bottles of 60.

JANUMET® is available for oral administration as tablets containing 64.25 mg sitagliptin phosphate monohydrate and metformin hydrochloride equivalent to: 50 mg sitagliptin as free base and 500 mg metformin hydrochloride (JANUMET® 50 mg/500 mg), 850 mg metformin hydrochloride (JANUMET® 50 mg/850 mg) or 1000 mg metformin hydrochloride (JANUMET® 50 mg/1000 mg).

Each film-coated tablet of JANUMET® contains the following inactive ingredients: microcrystalline cellulose, polyvinylpyrrolidone, sodium lauryl sulfate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and black iron oxide.

JANUMET® XR

Tablets JANUMET® XR, 50 mg/500 mg, are light blue, bi-convex oval, film coated tablet, debossed "78" on one side and plain on the other. They are supplied in bottles of 60.

Tablets JANUMET® XR, 50 mg/1000 mg, light green, bi-convex oval, film coated tablet, debossed "80" on one side and plain on the other. They are supplied in bottles of 60.

Tablets JANUMET® XR, 100 mg/1000 mg, blue, bi-convex oval, film coated tablet, debossed "81" on one side and plain on the other. They are supplied in bottles of 30.

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.

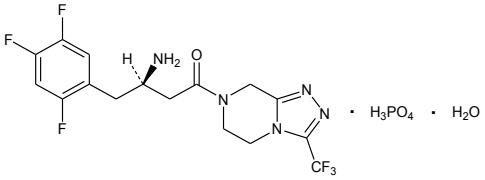
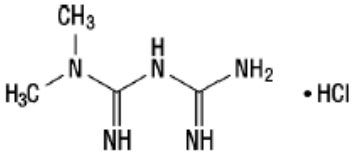
JANUMET® XR is available for oral administration as tablets containing 64.25 mg sitagliptin phosphate monohydrate (equivalent to 50 mg sitagliptin as free base) and either 500 mg metformin hydrochloride extended-release (JANUMET® XR 50 mg/500 mg) or 1000 mg metformin hydrochloride extended-release (JANUMET®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

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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name/ Proper name:	sitagliptin phosphate monohydrate	metformin hydrochloride
Chemical name:	7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate.	*N*,*N*-dimethyl biguanide hydrochloride
Molecular formula:	$C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$	$C_4H_{11}N_5 \cdot HCl$
Molecular mass:	523.32	165.63
Structural formula:		
Physicochemical properties:	Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.	Metformin hydrochloride is a white to off-white crystalline compound. It is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

CLINICAL TRIALS

Clinical studies of the coadministration of sitagliptin and metformin demonstrated significant improvements in glycemic control in patients with type 2 diabetes. None of the clinical efficacy studies described below were 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 (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Regimens of extended-release 500 mg metformin were at least as effective as corresponding regimens of an immediate-release 500 mg metformin in all measures of glycemic control. Additionally, once daily administration of two 500 mg extended-release metformin tablets was as effective as the commonly prescribed twice daily administration of the 500 mg immediate-release metformin formulation.

The combination of sitagliptin and metformin has been evaluated for safety and efficacy in four double-blind, placebo-controlled studies and in one double-blind, active controlled clinical study in patients with type 2 diabetes mellitus. In all studies, patients with inadequate glycemic control on stable doses of metformin ≥1500 mg were randomized to receive either sitagliptin 100 mg per day, or placebo or an active comparator, in addition to ongoing background therapy.

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

In combination with metformin, sitagliptin provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo with metformin (Table 7). The improvement in HbA_{1c} was not affected by baseline HbA_{1c}, prior anti-hyperglycemic therapy, gender, age, baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome (according to NCEP criteria), or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA-β). Body weight decreased from baseline in both treatment groups.

Table 7 – Glycemic parameters and body weight at final visit (24-week study) for sitagliptin in combination with metformin[†]

	Sitagliptin 100 mg + Metformin	Placebo + Metformin
HbA_{1c} (%)	**N=453**	**N=224**
Baseline (mean)	8.0	8.0
Change from baseline (adjusted mean[‡])	-0.7	-0.0
Difference from placebo + metformin (adjusted mean[‡])	-0.7[§]	
Patients (%) achieving HbA_{1c} <7%	213 (47.0%)	41 (18.3%)
FPG (mmol/L)	**N=454**	**N=226**
Baseline (mean)	9.4	9.6
Change from baseline (adjusted mean[‡])	-0.9	0.5
Difference from placebo + metformin (adjusted mean[‡])	-1.4[§]	
2-hour PPG (mmol/L)	**N=387**	**N=182**
Baseline (mean)	15.3	15.1
Change from baseline (adjusted mean[‡])	-3.4	-0.6
Difference from placebo + metformin (adjusted mean[‡])	-2.8[§]	
Body Weight (kg)[%]	**N=399**	**N=169**
Baseline (mean)	86.9	87.6
Change from baseline (adjusted mean[‡])	-0.7	-0.6
Difference from placebo + metformin (adjusted mean[‡])	-0.1[¶]	

[†] All Patients Treated Population (an intention-to-treat analysis).
[‡] Least squares means adjusted for prior antihyperglycemic therapy and baseline value.
[§] $p<0.001$ compared to placebo + metformin.
[%] All Patients as Treated (APaT) population, excluding patients given glycemic rescue therapy.
[¶] Not statistically significant ($p\geq0.05$) compared to placebo + metformin.

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

Both treatments resulted in a statistically significant improvement in glycemic control from baseline. After 52 weeks, the reduction from baseline in HbA_{1c} was 0.67% for sitagliptin 100 mg daily and 0.67% for glipizide, confirming the non-inferiority of sitagliptin compared to glipizide. The reduction in FPG was 0.6 mmol/L for sitagliptin and 0.4 mmol/L for glipizide. In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with sitagliptin relative to glipizide. The incidence of hypoglycemia in the sitagliptin group (4.9%) was significantly 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).

Add-on Combination Therapy with Metformin plus Glimepiride: In a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin 100 mg once daily (N=116) compared to placebo (N=113), 229 patients were on the combination of glimepiride (≥4 mg per day) and metformin (≥1500 mg per day); the results of the glycemic endpoints, including HbA_{1c} and FPG, are described below.

The combination of sitagliptin, glimepiride, and metformin provided significant reduction from baseline in HbA_{1c} and FPG compared to placebo (see Table 8). Mean reductions from baseline in HbA_{1c} compared with placebo were generally greater for patients with higher baseline HbA_{1c} values. Patients treated with sitagliptin, had a modest increase in body weight (0.4 kg) compared to those given placebo who had a significant decrease in body weight (-0.7 kg).

Table 8 – Glycemic Parameters and Body Weight at Final Visit (24-Week Study) for sitagliptin in Add-on Combination Therapy with Metformin plus Glimepiride[†]

	Sitagliptin 100 mg + Metformin + Glimepiride	**Placebo + Metformin + Glimepiride**
HbA_{1c} (%)	**N=115**	**N=105**
Baseline (mean)	8.27	8.28
Change from baseline (adjusted mean[‡])	-0.59	0.30
Difference from placebo (adjusted mean[‡])	-0.89[§]	
Patients (%) achieving HbA_{1c} <7%	26 (22.6)	1 (1.0)
FPG (mmol/L)	**N=115**	**N=109**
Baseline (mean)	9.95	9.93
Change from baseline (adjusted mean[‡])	-0.43	0.72
Difference from placebo (adjusted mean[‡])	-1.15[§]	
Body Weight (kg)[%]	**N=102**	**N=74**
Baseline (mean)	86.5	84.6
Change from baseline (adjusted mean[‡])	0.4	-0.7
Difference from placebo (adjusted mean[‡])	1.1[††]	

[†] All Patients Treated Population (an intention-to-treat analysis).
[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
[§] p<0.001 compared to placebo.
[%] All Patients as Treated (APaT) population, excluding patients given glycemic rescue therapy.
[††]p=0.007 compared to placebo.

Sitagliptin in Combination with 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 100 mg once daily in combination with insulin.

Approximately 75% (n=462) of patients were also taking metformin. Patients with an HbA_{1c} of 7.5% to 11.0% while on a stable regimen of pre-mixed, long-acting or intermediate acting insulin, and metformin (≥1500 mg per day) were randomized to the addition of either 100 mg of sitagliptin or placebo. Patients using pre-meal short-acting or rapid-acting insulins that were not components of a pre-mixed insulin formulation, or that were administered via insulin pumps, were not included in this study. Glycemic endpoints measured included HbA_{1c}, FPG and 2-hour PPG. The combination of sitagliptin, metformin and insulin provided significant improvements in HbA_{1c}, FPG and 2-hour PPG compared to placebo, metformin and insulin (Table 9). There was no meaningful change from baseline in body weight in either group.

Table 9 – Glycemic Parameters and Body Weight at Final Visit (24-Week Study) for Sitagliptin as Add-on Combination Therapy with Metformin and Insulin[†]

	Sitagliptin 100 mg + Insulin + Metformin	**Placebo + Insulin + Metformin**
HbA_{1c} (%)	N=223	N=229
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean[‡])	-0.7	-0.1
Difference from placebo (adjusted mean[‡, §])	-0.5[%]	
Patients (%) achieving HbA_{1c} <7%	32 (14.3)	12 (5.2)
FPG (mmol/L)	N=225	N=229
Baseline (mean)	9.6	9.8
Change from baseline (adjusted mean[‡])	-1.2	-0.2
Difference from placebo (adjusted mean[‡])	-1.0[%]	
2-hour PPG (mmol/L)	N=182	N=189
Baseline (mean)	15.6	15.6
Change from baseline (adjusted mean[‡])	-2.2	0.1
Difference from placebo (adjusted mean[‡])	-2.2[%]	
Body Weight (kg)[¶]	N=201	N=200
Baseline (mean)	87.9	88.0
Change from baseline (adjusted mean[‡])	-0.1	0.0
Difference from placebo (adjusted mean[‡])	-0.1[#]	

[†] All Patients Treated Population (an intention-to-treat analysis).
[‡] Least squares mean adjusted for insulin use at Visit 1 (premixed 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.
[¶] All Patients as Treated (APaT) population, excluding data following glycemic rescue therapy.
[#] Not statistically significant (p≥0.05) compared to placebo.

Add-on Combination Therapy with Metformin plus Pioglitazone: A total of 313 patients with type 2 diabetes participated in a 26-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with pioglitazone and metformin. Patients with inadequate glycemic control on a stable regimen of pioglitazone (30 or 45 mg per day) and metformin (≥1500 mg per day) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily.

In combination with pioglitazone and metformin, sitagliptin provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo with pioglitazone and metformin (Table 10). Lipid effects were generally neutral. The difference between sitagliptin and placebo in body weight change was not significant.

Table 10 – Glycemic Parameters and Body Weight at Final Visit (26-Week Study) for sitagliptin as Add-on Combination Therapy with Pioglitazone and Metformin[†]

	Sitagliptin 100 mg + Pioglitazone 30 or 45 mg + Metformin	**Placebo + Pioglitazone 30 or 45 mg + Metformin**
HbA_{1c} (%)	**N=152**	**N=153**
Baseline (mean)	8.8	8.6
Change from baseline (adjusted mean[‡])	-1.2	-0.4
Difference from placebo (adjusted mean[‡])	-0.7[§]	
Patients (%) achieving HbA_{1c} <7%	38 (25.0)	15 (9.8)
FPG (mmol/L)	**N=155**	**N=153**
Baseline (mean)	10.0	9.6
Change from baseline (adjusted mean[‡])	-1.1	-0.2
Difference from placebo (adjusted mean[‡])	-1.0[§]	
2-hour PPG (mmol/L)	**N=141**	**N=135**
Baseline (mean)	15.3	14.7
Change from baseline (adjusted mean[‡])	-3.0	-0.8
Difference from placebo (adjusted mean[‡])	-2.2[§]	
Body Weight (kg)[%]	**N=146**	**N=128**
Baseline (mean)	81.4	82.0
Change from baseline (adjusted mean[‡])	1.3	1.1
Difference from placebo (adjusted mean[‡])	0.1[¶]	

[†] Full Analysis Set population (an intention-to-treat analysis).
[‡] Least squares mean adjusted for baseline value.
[§] p<0.001 compared to placebo.
[%] All Patients as Treated (APaT) population, excluding data following glycemic rescue therapy.
[¶] Not statistically significant (p≥0.05) compared to placebo.

TECOS Cardiovascular Safety Study

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a randomized, double-blind, placebo-controlled, parallel-group, event-driven, multicentre study in patients with type 2 diabetes mellitus (HbA1c ≥6.5 to 8.0%) and established vascular disease (coronary artery disease, ischemic cerebrovascular disease, atherosclerotic peripheral artery disease). The study included 14,671 patients (70.7% male, 29.3% female) in the intention-to-treat population who received sitagliptin (N=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 (N=7,339) added to usual care targeting regional standards for HbA1c and CV risk factors. The median duration of treatment was 31 months and the median duration of follow-up was 36 months. Patients with an eGFR <30 mL/min/1.73 m^2 were not to be enrolled in the study. The study population included 10,863 patients with coronary artery disease, 3,588 patients with cerebrovascular disease, 2,433 patients with peripheral artery

disease, 2,643 patients with prior congestive heart failure (including 373 with New York Heart Association [NYHA] class 3 or higher), 2,004 patients ≥75 years of age and 3,324 patients with renal impairment (eGFR <60 mL/min/1.73 m^2).

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina. Secondary cardiovascular endpoints included a composite of the first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke; as well as first occurrence of the following independent CV endpoints: cardiovascular death, myocardial infarction (fatal + non-fatal), stroke (fatal + non-fatal), hospitalization for unstable angina, hospitalization for heart failure, and all-cause mortality. A composite endpoint of first occurrence of death due to heart failure or hospitalization for congestive heart failure was also assessed.

Sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of death or hospitalization for heart failure compared to usual care without sitagliptin patients with type 2 diabetes. Superiority to placebo was not demonstrated for any endpoint (Table 11).

Table 11 -Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes Censored at End of Follow-up (Intention-to-Treat Population)

	Sitagliptin (N=7,332)		Placebo N=7,339)			
	Subjects with Events N (%)	Incidence Rate per 100 Patient-Years*	Subjects with Events N (%)	Incidence Rate per 100 Patient-Years*	Hazard Ratio (95% CI)	p-value†
Primary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2	0.98 (0.89, 1.08)	<0.001
Secondary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, or non-fatal 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
Death due to heart failure or hospitalization for heart failure‡	237 (3.2)	1.1	240 (3.3)	1.1	0.99 (0.83, 1.18)	0.909

* 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.

Metformin

The prospective randomized (UKPDS) study has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

– a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone

(43.3 events/1000 patient-years), p=0.0023, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), p=0.0034.

– a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, p=0.017. There was no significant difference between the metformin group and those assigned intensive therapy with sulfonylurea or insulin.

– a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years (p=0.011), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p=0.021).

– a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years (p=0.01). There was no significant difference between the metformin group and those assigned intensive therapy with sulfonylurea or insulin.

– There were no significant differences between the metformin group and the diet alone in the other aggregate endpoints (stroke, peripheral vascular disease and microvascular complications).

DETAILED PHARMACOLOGY

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

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

Metformin

Metformin absorption is relatively slow and may extend over about 6 hours. Animal studies with metformin, labelled with 14C have shown that the drug is neither concentrated by liver cells nor is it excreted in the bile; it is concentrated in the intestinal mucosa and salivary glands.

It has been shown that, following a 2 g dose of metformin, the blood level remains under 10 mcg/mL even at the peak, occurring 2 hours after absorption. During the experiments, metformin was shown to be devoid of any notable action in the body, apart from its specific metabolic activity.

In the healthy animal, metformin lowers blood sugar only at a nearly lethal dose. Different animal species are of unequal sensitivity. On the other hand, the animal with experimental diabetes, is sensitive to a much lower dosage, providing some insulin is still secreted.

The antihyperglycemic action of metformin is probably mediated through insulin:

Metformin improves the K co-efficient of glucose assimulation.
Metformin improves the co-efficient of insulin efficiency.

In the obese diabetic with hyperinsulinemia, metformin is reported to normalize insulin output. This normalizing effect is concurrent to that of glycemia.

Metformin has little effect on liver glycogen of the healthy animal. In low and average doses, no change occurs. In high doses nearing lethal levels, liver glycogen decreases. This lowering precedes the fall in blood sugar. This reaction represents a defense mechanism tending to mobilize body reserves in order to combat hypoglycemia.

In the diabetic animal with a low liver glycogen reserve, the opposite occurs and metformin builds up glycogen stores of the liver. *In vitro*, on muscular tissue isolated in Warburg's apparatus, metformin increases glucose uptake by the muscle. This action follows an aerobic pathway. Even in high concentration, contrary to phenethyl-biguanide, metformin apparently does not block respiration or change carbohydrate metabolism via the anaerobic pathway.

Metformin is eliminated in faeces and urine. It is rapidly excreted by the kidneys in an unchanged form.

Renal clearance is 450 mL/minute; this appears to explain the absence of accumulation.

Metabolites of metformin have not been identified, neither by radio-active nor by chemical methods.

A single Rf spot is always present following radiochromatographic study of urine and always corresponds to that of pure metformin. Administration during 10 consecutive days has not shown any sign of accumulation.

Inhibition of glyconeogenesis has been observed in animals following its stimulation by fasting, cortisol, alcohol or other substrates such as alanine lactate or pyruvate. However, such an effect varies according to the type and dosage of the biguanide used, nutritional state of the animal species and design of experimental model.

This inhibition of glyconeogenesis is observed only in the presence of insulin and it does not appear to play an important role in man.

Inhibition of intestinal absorption of sugars, which is not related to a malasorption phenomenon has been observed with biguanides under certain experimental conditions in animal and in man. In one study, a 20% retardation of galactose absorption was observed in man receiving metformin. However, such an effect of metformin could not be confirmed in another study in man.

Recent findings appear to indicate that most of the metabolic effects of the biguanides are exerted through a single mechanism, namely inhibition of fatty acid oxidation and of acetyl-CoA generation.

However, inhibition of insulin-stimulated lipogenesis which has also been observed appears to be due to the inhibition of acetyl-CoA carboxylase by the biguanides. Such an effect may explain, at least partly, the weight-reducing effect exerted by these drugs in obese diabetic patients.

TOXICOLOGY

JANUMET® and JANUMET® XR

No animal studies have been conducted with the combined products in JANUMET® or JANUMET® XR to evaluate carcinogenesis, mutagenesis, impairment of fertility or effects on reproduction. The following data are based on the findings in studies with sitagliptin and metformin individually and a 16 week toxicity study in dogs with the concomitant administration of sitagliptin and metformin.

Acute Toxicity

Sitagliptin

The approximate LD_{50} of sitagliptin given orally to rats is >3000 mg/kg (maximum dose tested). This dose is equivalent to ≥200 times the human exposure based on the recommended daily adult human dose of 100 mg/day. In mice the approximate oral LD_{50} of sitagliptin is 4000 mg/kg. This dose is equivalent to >385 times the human exposure based on recommended daily adult human dose of 100 mg/day.

Chronic Toxicity

Sitagliptin and Metformin

Preclinical toxicokinetic and oral toxicity studies in dogs have been conducted with the combined products in JANUMET®.

In a sixteen-week oral toxicity study, female dogs were administered 20 mg/kg/day of metformin, alone or in combination with 2, 10, or 50 mg/kg/day of sitagliptin. Transient ataxia and/or tremors were observed in the high-dose combination-treatment group. These signs were considered to be an effect of sitagliptin because they were seen in previous dog studies with sitagliptin alone at 50 mg/kg/day. The no-effect level for treatment-related changes in this study was 10 mg/kg/day of sitagliptin plus 20 mg/kg/day of metformin, which provided systemic exposure to sitagliptin of approximately 6 times that in patients treated with 100 mg/day of sitagliptin and systemic exposure to metformin of approximately 2.5 times that in patients treated with 2000 mg/day of metformin.

Sitagliptin

The toxicity potential of sitagliptin was evaluated in a series of repeated dose toxicity studies of up to 53 weeks in dogs and up to 27 weeks in rats. In dogs administered sitagliptin orally at dosages of 2, 10 and 50 mg/kg/day, the no-observed effect level was 10 mg/kg/day (up to 6 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Treatment-related physical signs observed in the 50-mg/kg/day group included open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture. These signs were transient, slight in degree, and occurred with decreased incidence during the course of the study. In addition, very slight to slight skeletal muscle degeneration was observed histologically in the 14- and 27-week toxicity studies at the 50-mg/kg/day dose. However, no skeletal muscle degeneration was found in the 53-week toxicity study, indicating the lack of reproducibility or progression of this change with increased duration of treatment. The 50-mg/kg/day dose in dogs resulted in systemic exposure values 26 times the human exposure at the recommended daily adult human dose of 100 mg/day. In rats, sitagliptin administered orally at dosages of up to 180 mg/kg/day (up to 23 times the human exposure based on the recommended daily adult human dose of 100 mg/day), no significant toxicity was observed. The only drug-related effect observed was postdose salivation, likely related to poor palatability of the drug, at doses of 60 mg/kg/day and 180 mg/kg/day.

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

Metformin

In a 26-week oral toxicity study in rats, decrease in body weight gains were observed at 450 and 900 mg/kg/day, and changes in clinical laboratory parameters (decreased total leukocyte, lymphocyte and neutrophil count) and in some organ weights were noted at 900 mg/kg/day. The no-observed-adverse-effect level was 150 mg/kg/day (approximately 1.5 times the maximum recommended human daily dose based on body surface area comparisons).

In a 39-week oral toxicity study in dogs, treatment-related effects in food consumption were limited to females at 80 mg/kg/day. The no-observed-adverse-effect level was 80 mg/kg/day (approximately 2.6 times the maximum recommended human daily dose based on body surface area comparisons).

Carcinogenicity

Sitagliptin

A two-year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of hepatic adenomas and carcinomas in the high-dose males and hepatic carcinomas in the high-dose females. This dose in rats results in approximately 58 times the human exposure based on the recommended daily adult human dose of 100 mg/day. This dose level was associated with hepatotoxicity in rats. The no-observed effect level for induction of hepatic neoplasia was 150 mg/kg/day, approximately 19-fold the human exposure at the 100-mg recommended dose. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this

increased incidence of hepatic tumors in rats was likely secondary to chronic hepatic toxicity at this high dose. The clinical significance of these findings for humans is unknown.

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

Metformin

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately three times the maximum recommended human daily dose based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

A carcinogenicity study was also conducted via dermal administration in Tg.AC transgenic mice at doses up to and including 2000 mg/kg/day. No evidence of carcinogenicity was observed in either male or female mice.

Mutagenesis

Sitagliptin

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

Metformin

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Reproduction

Sitagliptin

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

Metformin

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

A decrease in male reproductive organ weights was observed at higher oral dose of 900 mg/kg/day in a fertility and developmental toxicity study in rats.

Development

JANUMET®

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

Sitagliptin

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

Metformin

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

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PART III: CONSUMER INFORMATION

PrJANUMET®

sitagliptin and metformin hydrochloride tablets (as sitagliptin phosphate monohydrate and metformin hydrochloride)

PrJANUMET® XR

sitagliptin and metformin hydrochloride modified-release tablets (as sitagliptin phosphate monohydrate and metformin hydrochloride)

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

ABOUT THIS MEDICATION

What the medication is used for:
JANUMET® or JANUMET® XR are used in addition to diet and exercise to improve blood sugar levels in patients with type 2 diabetes mellitus

- Alone, in patients who are not controlled on metformin alone or currently on sitagliptin (JANUVIA®) and metformin; OR
- In combination with a sulfonylurea, in patients who are not controlled on metformin and a sulfonylurea.
- JANUMET® or JANUMET® XR can be taken with premixed or long/intermediate acting insulin.
- In combination with pioglitazone, in patients who are not controlled on metformin and pioglitazone.

What it does:
JANUMET® and JANUMET® XR are a tablet that contains sitagliptin and metformin. These two medicines work together to help you achieve better blood sugar control.

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

Metformin is a member of the biguanide class of medicines, it helps to lower the amount of sugar made by the liver. Together, these medicines help you to achieve better blood sugar control.

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

When it should not be used:
Do not take JANUMET® or JANUMET® XR if you:

- Have unstable and/or insulin-dependent (Type 1) diabetes mellitus
- Have metabolic acidosis (including diabetic ketoacidosis, history or ketoacidosis or lacticacidosis – too much acid in the blood)
- Have a liver or kidney problems
- Drink a lot of alcohol
- Have cardiovascular collapse (abrupt failure of blood circulation) or cardiorespiratory insufficiency
- Are stressed, have severe infections, are experiencing trauma, prior to surgery or during the recovery phase
- Suffer from severe dehydration (have lost a lot of water from your body)
- Are allergic to sitagliptin, metformin, or any of the ingredients in JANUMET® or JANUMET® XR. See "What the important non-medicinal ingredients are"
- Are breastfeeding
- Are pregnant or planning to become pregnant
- Are going to get or receive an injection of dye or contrast agent for an x-ray procedure. Talk to your physician or pharmacist about when to stop JANUMET® or JANUMET® XR and when to start again

What the medicinal ingredients are:
sitagliptin phosphate monohydrate and metformin hydrochloride

What the non-medicinal ingredients are:
Each film-coated tablet of JANUMET® contains the following inactive ingredients: microcrystalline cellulose, polyvinylpyrrolidone, sodium lauryl sulfate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and black iron oxide.

Each modified-release tablet of JANUMET® XR contains the following inactive ingredients: colloidal silicon dioxide, hypromellose, kaolin, polyethylene glycol, povidone, propyl gallate, and sodium stearyl fumarate. 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.

What dosage forms it comes in:
JANUMET® contains sitagliptin/metformin hydrochloride 50 mg/500 mg, 50 mg/850 mg, or 50 mg/1000 mg.

JANUMET® XR contains immediate release sitagliptin (as sitagliptin phosphate monohydrate) /extended release metformin hydrochloride 50 mg/500 mg, 50 mg/1000 mg or 100 mg/1000 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

JANUMET® and JANUMET® XR contains metformin which can rarely cause lactic acidosis. Lactic acidosis can cause death and must be treated in the hospital (see section Lactic Acidosis below). Since alcohol may increase the risk of lactic acidosis caused by metformin you should not drink a lot of alcohol if you take JANUMET® and JANUMET® XR (see section Lactic Acidosis below).

Lactic Acidosis

Stop taking JANUMET® or JANUMET® XR if you get the following symptoms of lactic acidosis:

- You feel very weak and tired.
- You have unusual (not normal) muscle pain.
- You have trouble breathing.
- You have stomach pain with nausea and vomiting, or diarrhea.
- You feel cold, especially in your arms and legs.
- You feel dizzy or lightheaded.
- You have a slow or irregular heartbeat.
- Your medical condition suddenly changes.

You have a higher chance of getting lactic acidosis if you:

- Have kidney problems.
- Have congestive heart failure that requires treatment with medicines.
- Drink a lot of alcohol (very often or short-term "binge" drinking).
- Get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and don't drink enough fluids.
- Have certain x-ray tests with injectable dyes or contrast agents used.
- Have surgery.
- Have a heart attack, severe infection, or stroke.
- Are 80 years of age or older and have not had your kidney function tested.

Cases of inflammation of the pancreas (pancreatitis) which may be severe and lead to death have been reported in patients taking JANUMET® or JANUMET® XR.

Cases of a skin reaction called bullous pemphigoid that can require treatment in a hospital have been reported in patients receiving JANUMET® or JANUMET® XR. Tell your doctor if you develop blisters or the breakdown of your skin (erosion). Your doctor may tell you to stop taking JANUMET® or JANUMET® XR.

BEFORE or while taking JANUMET® or JANUMET® XR talk to your physician or pharmacist if:

- You have or have had pancreatitis (inflammation of the pancreas) or any risk factors for pancreatitis such as gallstones (solid particles that form in the gall bladder), a history of alcoholism, high triglyceride levels.
- You are receiving treatment with insulin since this drug can increase the risk of hypoglycemia (low blood sugar). When JANUMET® or JANUMET® XR is used in combination with sulfonylurea or insulin, low blood sugar can occur. Your physician may consider lowering the dose of the sulfonylurea or insulin. Take precautions to avoid low blood sugar while driving or using machinery.
- You have or have had an allergic reaction to sitagliptin, metformin, JANUMET® or JANUMET® XR.
- You have heart problems including congestive heart failure (a condition where your heart becomes weaker and less able to pump the blood that your body needs).
- You have or have had kidney problems.
- You have liver problems.
- Drink alcohol a lot (all the time or short-term "binge" drinking).
- You are pregnant or plan to become pregnant. JANUMET® or JANUMET® XR are not recommended for use during pregnancy.
- You are breast-feeding or plan to breast-feed. You should not use JANUMET® or JANUMET® XR if you are breast feeding. It is not known if JANUMET® or JANUMET®XR passes into breast milk.
- Are older than 80 years. Patients over 80 years should not take JANUMET® or JANUMET® XR unless their kidney function is checked and it is normal.

JANUMET® or JANUMET® XR may cause abnormal kidney function. Your doctor will do blood tests to monitor how well your kidneys are working while you are taking JANUMET® or JANUMET® XR.

JANUMET® and JANUMET® XR are not recommended for use in children under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Some drugs may interact with JANUMET® or JANUMET® XR

Careful monitoring is advised. Tell your doctor if you are taking:

- other diabetes drugs such as glyburide
- furosemide
- nifedipine
- cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin)
- other drugs tend to produce hyperglycemia (high blood sugar) and may lead to a loss of blood sugar control. Some example of drugs that can increase the blood sugar include:

- Thiazide and other diuretics (water pills)
- Corticosteroids
- Phenothiazines
- Thyroid products
- Estrogens or estrogens plus progestogen
- Oral contraceptives
- Phenytoin
- Nicotinic Acid
- Sympathomimetics
- Calcium channel blocking drugs
- Isoniazid
- Beta-2-agonists

ACE inhibitors drugs may lower blood glucose and the combination with JANUMET® or JANUMET® XR should be carefully monitored.

Before using any drugs or herbal products, check with your physician or your pharmacist.

PROPER USE OF THIS MEDICATION

Take JANUMET® or JANUMET® XR exactly as your physician has prescribed. Your physician will tell you how many JANUMET® or JANUMET® XR tablets to take and how often you should take them.

Your physician may need to increase your dose to control your blood sugar.

Usual dose:
JANUMET® should generally be given twice daily with meals to lower your chance of an upset stomach.

JANUMET® XR should be taken once a day with food preferably in the evening to lower your chance of an upset stomach.

If you take JANUMET® XR, swallow the JANUMET® XR tablets whole. Do not chew, cut, or crush the tablets. Tell your doctor if you cannot swallow JANUMET® XR whole.

Very rarely, you may see something that looks like the JANUMET® XR tablet in your stool (bowel movement). If this happens, check your blood sugar. If your blood sugar control has changed, contact your doctor. Do not stop taking JANUMET® XR without talking to your doctor.

Continue to take JANUMET® or JANUMET® XR as long as your physician prescribes it so you can continue to help control your blood sugar.

You may need to stop JANUMET® or JANUMET® XR for a short time. Call your physician for instructions if you:

- have a condition that may be associated with dehydration (large loss of body fluids) such as being sick with severe vomiting, diarrhea or fever, or if you drink fluids a lot less than normal.
- plan to have surgery.
- are going to get or receive an injection of dye or contrast agent for an x-ray procedure.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take it with food as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of JANUMET® or JANUMET® XR at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, JANUMET® and JANUMET® XR may cause side effects.

The most common side effects in patients taking sitagliptin alone include: stuffy or runny nose and sore throat.

Common side effects of metformin include: diarrhea, nausea, upset stomach, abdominal bloating, gas, loss of appetite. Similar adverse experiences were seen in patients treated with extended-release metformin products.

In rare cases, metformin, one of the medicines in JANUMET® and JANUMET® XR can cause a serious side effect called lactic acidosis. This is caused by a buildup of lactic acid in your blood. This build-up can cause serious damage. You should also stop using JANUMET® or JANUMET® XR and call your physician right away if you have signs of lactic acidosis. Lactic acidosis is a medical emergency that must be treated in a hospital.

When JANUMET® or JANUMET® XR is used with a sulfonylurea medicine or with insulin, low blood sugar (hypoglycemia) can occur. Lower doses of the sulfonylurea medicine or insulin may be required while you used JANUMET® or JANUMET® XR. The signs and symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, confusion, irritability, hunger, fast heartbeat, sweating, and feeling jittery. Discuss with your physician or pharmacist how to treat low blood sugar.

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

Additional side effects have been reported in general use with JANUMET®, JANUMET® XR or sitagliptin, one of the medicines in JANUMET® or JANUMET® XR. These side effects have been

reported when JANUMET®, JANUMET® XR or sitagliptin have been used by themselves and/or with other diabetes medicines:

- Allergic reactions, which may be serious, including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing. If you have an allergic reaction, stop taking JANUMET® or JANUMET® XR and call your physician right away. Your physician may prescribe a medication to treat your allergic reaction and a different medication for your diabetes.
- Inflammation of the pancreas.
- Kidney problems (sometimes requiring dialysis).
- Constipation.
- Vomiting.
- Headache.
- Joint pain.
- Muscle aches.
- Arm or leg pain.
- Back pain.
- Itching
- Blisters

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

Symptoms / Effects	Talk with your physician or pharmacist		Stop taking drug and call your physician or pharmacist
	Only if severe	In all cases	
Very common			
Hypoglycemia (when used with a sulfonylurea or insulin)		✓	
Uncommon			
Feeling very weak, tired or uncomfortable; unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, suddenly developing a slow or irregular heartbeat			✓
Rare			
Pancreatitis: symptoms of pancreatitis (prolonged severe abdominal pain which may be accompanied by vomiting)		✓	✓
Allergic reactions including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing			✓
Bullous pemphigoid (blisters or breakdown of your skin)		✓	

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

Symptoms / Effects	Talk with your physician or pharmacist		Stop taking drug and call your physician or pharmacist
	Only if severe	In all cases	
Lactic Acidosis: Symptoms include feeling very weak, tired or uncomfortable; unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, unusual fatigue and drowsiness, or suddenly developing a slow or irregular heartbeat			✓
Acute kidney failure: symptoms may include nausea, loss of appetite and weakness, pass little or no urine, breathlessness		✓	

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

HOW TO STORE IT

The product should be stored at 15°C–30 °C.

Keep JANUMET®, JANUMET® XR and all medicines safely away from children.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect. (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php)

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice. »

To report an adverse event related to JANUMET®/ JANUMET® XR, please contact 1-800-567-2594.

MORE INFORMATION

If you want more information about JANUMET®/JANUMET® XR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website or Merck Canada website www.merck.ca or by calling Merck Canada at 1-800-567-2594.

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