JANUMET™ XR

(Sitagliptin phosphate – Metformin HCl extended-release 50/500, 50/1000, 100/1000 mg)

WARNING: LACTIC ACIDOSIS

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

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

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

INDICATIONS AND USAGE

- JANUMET XR is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus inadequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.
- JANUMET XR is also indicated in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients with type 2 DM inadequately controlled with any two of the three agents: metformin, sitagliptin, or a sulfonylurea.
- JANUMET XR is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycemic control.

When JANUMET XR is used in combination with sulfonylurea or with insulin, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

DOSAGE AND ADMINISTRATION

Recommended Dosing

The dosage of antihyperglycemic therapy with JANUMET XR should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin.

When JANUMET XR is used in combination with sulfonylurea or with insulin, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

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

The following doses are available:
50 mg sitagliptin/500 mg extended-release metformin hydrochloride
50 mg sitagliptin/1000 mg extended-release metformin hydrochloride
100 mg sitagliptin/1000 mg extended-release metformin hydrochloride

For patients currently using 100 mg sitagliptin and 1000 mg metformin hydrochloride per day, the 100 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablet should be taken as a single tablet once daily.

The formulations containing 50 mg sitagliptin can be used to gradually escalate the dose of JANUMET XR:

- For patients requiring 1500 mg metformin per day, a patient should take one of the 50 mg sitagliptin/500 mg metformin hydrochloride extended-release tablets and one of the 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets once daily
- For patients requiring 2000 mg metformin per day, a patient should take two of the 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets together once daily.

Patients inadequately controlled on metformin monotherapy

For patients not adequately controlled on metformin alone, the usual starting dose of JANUMET XR should be equal to 100 mg total daily dose (once daily) of sitagliptin plus the dose of metformin already being taken.

Patients inadequately controlled on sitagliptin monotherapy

For patients inadequately controlled on sitagliptin alone, the recommended starting dose of JANUMET XR is 100 mg sitagliptin and 1000 mg metformin hydrochloride. The metformin dose can be titrated as needed to achieve glycemic control. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered.

Patients taking sitagliptin monotherapy dose-adjusted for renal impairment should not be switched to JANUMET XR *[see Contraindications]*.

Patients switching from sitagliptin co-administered with metformin

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

For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin

The dose should provide 100 mg sitagliptin and a dose of metformin similar to the dose already being taken. When JANUMET XR is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia.

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

Recommendations for use in renal impairment:

Assess renal function prior to initiation of JANUMET XR and periodically thereafter.

No dose adjustment is needed for patients with mild renal impairment (estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 m^2 and < 90 mL/min/1.73 m^2).

For patients with moderate renal impairment (eGFR ≥45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2), the maximum daily dose is 1000 mg of metformin, and the starting dose is 500 or 750 mg of metformin. The maximum daily dose of sitagliptin is 100 mg.

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

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

Pediatric Patients

JANUMET XR is not indicated in pediatric patients 10 to 17 years old with type 2 diabetes. JANUMET XR has not been studied in pediatric patients under 10 years of age.

CONTRAINDICATIONS

JANUMET XR (sitagliptin/metformin HCl extended release) is contraindicated in patients with:

- Severe renal impairment, (eGFR < 30 mL/min/1.73 m^2) (see **WARNINGS AND PRECAUTIONS**,

Monitoring of Renal Function).

- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- History of serious hypersensitivity reaction to JANUMET XR, sitagliptin, metformin HCl or any other components of JANUMET XR such as anaphylaxis or angioedema (see Warnings and Precautions and Adverse Reactions)

JANUMET XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Lactic Acidosis

Metformin hydrochloride

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with 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). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications (see *Dosage And Administration*, *Recommendations for use in renal impairment*). Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function (see *Use In Specific Populations, Geriatric Use, Metformin hydrochloride*). In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol

intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure *[see Warnings and Precautions]*.

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 *[see Warnings and Precautions]*. 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 *[see Warnings and Precautions]*.

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; Warnings and Precautions]*.

Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis (see Adverse Reactions), in patients taking sitagliptin. After initiation of JANUMET XR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUMET XR should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUMET XR.

Impaired Hepatic Function

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

Monitoring of Renal Function

Metformin and sitagliptin are known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. JANUMET XR is contraindicated in severe renal impairment, patients with an eGFR < 30 mL/min/1.73 m^2 (see *Dosage And Administration*, *Contraindications* and *Warnings and Precautions*, *Metformin hydrochloride*, Lactic acidosis).

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

Vitamin B_{12} Levels

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

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

Alcohol Intake

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

Surgical Procedures

Use of JANUMET XR should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as acceptable (see *Dosage And Administration*).

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes

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

Use with Medications Known to Cause Hypoglycemia

Sitagliptin

When sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause

hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin [see Adverse Reactions]. Therefore, patients also receiving an insulin secretagogue (e.g., sulfonylurea) or insulin may require a lower dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia [see Dosage and Administration].

Metformin hydrochloride

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.

Concomitant Medications Affecting 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 with Intravascular Iodinated Contrast Materials

Intravascular contrast studies with iodinated materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin *[see Contraindications]*. Therefore, in patients with an eGFR ≥ 30 to < 60 mL/min/1.73 m^2, in patients with a history of hepatic impairment, alcoholism, or heart failure, or in patients who will be administered intra-arterial iodinated contrast, JANUMET XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been reevaluated and found to be acceptable (see *Dosage And Administration*).

Hypoxic States

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

Loss of Control of Blood Glucose

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

Hypersensitivity reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with

sitagliptin, one of the components of JANUMET XR. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or established a causal relationship to drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUMET XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. *[See Adverse Reactions]*

Macrovascular outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET XR or any other anti-diabetic drug.

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

Bullous Pemphigoid

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

ADVERSE REACTIONS

Clinical Trials Experience

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

Sitagliptin and Metformin Co-administration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise

Table 1 summarizes the most common (≥5% of patients) adverse reactions reported (regardless of investigator assessment of causality) in a 24-week placebo-controlled factorial study in which sitagliptin and metformin were co-administered to patients with type 2 diabetes inadequately controlled on diet and exercise.

Table 1: Sitagliptin and Metformin Co-administered to Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)†				
	Number of Patients (%)			
	Placebo	Sitagliptin 100 mg QD	Metformin 500 mg/ Metformin 1000 mg bid ††	Sitagliptin 50 mg bid + Metformin 500 mg/ Metformin 1000 mg bid ††
	N = 176	N = 179	N = 364††	N = 372††
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)
Upper Respiratory Tract Infection	9 (5.1)	8 (4.5)	19 (5.2)	23 (6.2)
Headache	5 (2.8)	2 (1.1)	14 (3.8)	22 (5.9)

† Intent-to-treat population.

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

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

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

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

Table 2: Pre-selected Gastrointestinal Adverse Reactions (Regardless of Investigator Assessment of Causality) Reported in Patients with Type 2 Diabetes Receiving Sitagliptin and Metformin	
	Number of Patients (%)

	Study of Sitagliptin and Metformin in Patients Inadequately Controlled on Diet and Exercise				Study of Sitagliptin Add-on in Patients Inadequately Controlled on Metformin Alone	
	Placebo	Sitagliptin 100 mg QD	Metformin 500 mg/ Metformin 1000 mg bid †	Sitagliptin 50 mg bid + Metformin 500 mg/ Metformin 1000 mg bid †	Placebo and Metformin ≥1500 mg daily	Sitagliptin 100 mg QD and Metformin ≥1500 mg daily
	N = 176	N = 179	N = 364	N = 372	N = 237	N = 464
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)	6 (2.5)	11 (2.4)
Nausea	2 (1.1)	2 (1.1)	20 (5.5)	18 (4.8)	2 (0.8)	6 (1.3)
Vomiting	1 (0.6)	0 (0.0)	2 (0.5)	8 (2.2)	2 (0.8)	5 (1.1)
Abdominal Pain††	4 (2.3)	6 (3.4)	14 (3.8)	11 (3.0)	9 (3.8)	10 (2.2)

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

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

Sitagliptin in Combination with Metformin and Glimepiride

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

Sitagliptin in Combination with Metformin and Insulin

In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin and stable-dose insulin (sitagliptin, N=229; placebo, N=233), the only adverse reaction reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycemia (Table 3). In another 24-week study of patients receiving sitagliptin as add-on therapy while undergoing insulin intensification (with or without metformin), the only drug-related adverse reaction reported in ≥1% in patients treated with sitagliptin and metformin and more commonly than in patients treated with placebo and metformin was vomiting (sitagliptin and metformin, 1.1%; placebo and metformin, 0.4%).

Hypoglycemia

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

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

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

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

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

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

The overall incidence of reported adverse reactions of hypoglycemia in patients with type 2 diabetes inadequately controlled on diet and exercise was 0.6% in patients given placebo, 0.6% in patients given sitagliptin alone, 0.8% in patients given metformin alone, and 1.6% in patients given sitagliptin in combination with metformin. In patients with type 2 diabetes inadequately controlled on metformin alone, the overall incidence of adverse reactions of hypoglycemia was 1.3% in patients given add-on sitagliptin and 2.1% in patients given add-on placebo.

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

In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of non-adjudicated acute pancreatitis events was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control). See also *TECOS Cardiovascular Safety Study* below *[See Warnings and Precautions]*

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

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

TECOS Cardiovascular Safety Study

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

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 2.7% in sitagliptin-treated patients and 2.5% in placebo-treated

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

Pediatric population

In clinical trials with Janumet in paediatric patients with type 2 diabetes mellitus aged 10 to 17 years, the profile of adverse reactions was generally comparable to that observed in adults. In paediatric patients on or not on background insulin, sitagliptin was associated with an increased risk of hypoglycaemia.

Laboratory Tests

Sitagliptin

The incidence of laboratory adverse reactions was similar in patients treated with sitagliptin and metformin (7.6%) compared to patients treated with placebo and metformin (8.7%). In most but not all studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to a small increase in neutrophils. This change in laboratory parameters is not considered to be clinically relevant.

Metformin hydrochloride

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

Post Marketing Experience

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

Hypersensitivity reactions, including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis and exfoliative skin condition including Stevens-Johnson syndrome (see *Warnings and Precaution*); upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis *[see Limitations of Use; Warnings and Precautions]*; constipation; vomiting; headache; worsening renal function; including acute failure (sometimes requiring dialysis); bullous pemphigoid (see *Warnings And Precautions*, Bullous Pemphigoid); arthralgia; myalgia; pain in extremity;

back pain; pruritus.

DRUG INTERACTIONS

Drugs that reduce metformin clearance

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

Digoxin

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C_{max}, 18%) of digoxin with the co-administration of 100 mg sitagliptin for 10 days. These increases are not considered likely to be clinically meaningful. Digoxin, as a cationic drug, has the potential to compete with metformin for common renal tubular transport systems, thus affecting the serum concentrations of either digoxin, metformin or both. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or JANUMET XR is recommended.

Glyburide

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

Furosemide

A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine

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

The Use of Metformin with Other Drugs

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs

include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JANUMET XR the patient should be closely observed to maintain adequate glycemic control.

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

JANUMET XR

There are no adequate and well-controlled studies in pregnant women with JANUMET XR or their individual components; therefore, the safety of JANUMET XR in pregnant women is not known. JANUMET XR should be used during pregnancy only if clearly needed.

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

Sitagliptin

Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies with sitagliptin in pregnant women.

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

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

Metformin hydrochloride

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

Nursing Mothers

No studies in lactating animals have been conducted with the combined components of JANUMET XR. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUMET XR is administered to a nursing woman.

Pediatric Use

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

While superiority of HbA_{1c} reduction was demonstrated for JANUMET/JANUMET XR over metformin at Week 20 in the pooled analysis of these two studies, results from the individual studies were inconsistent. Furthermore, efficacy for JANUMET/JANUMET XR over metformin was not observed at Week 54. Therefore, these results do not support use of JANUMET or JANUMET XR in pediatric subjects (10 to 17 years old) with type 2 diabetes.

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

Geriatric Use

JANUMET XR

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

Sitagliptin

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

younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients.

OVERDOSAGE

Sitagliptin

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Maximal mean increases in QTc of 8.0 msec were observed in one study at a dose of 800 mg sitagliptin, a mean effect that is not considered clinically important *[see Clinical Pharmacology]*. There is no experience with doses above 800 mg in humans. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 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 as indicated by the patient's clinical status.

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

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases *[see Warnings and Precautions]*. 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.

CLINICAL PHARMACOLOGY

Mechanism of Action

JANUMET XR

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

Sitagliptin

Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased

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

Metformin hydrochloride

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances *[see Warnings and Precautions]*) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacodynamics

Sitagliptin

General

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

Sitagliptin and Metformin hydrochloride Co-administration

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. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear what these findings mean for changes in glycemic control in patients with type 2 diabetes.

In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.

Cardiac Electrophysiology

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

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

Pharmacokinetics

JANUMET XR

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

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

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 Tmax values for sitagliptin and metformin at steady state were approximately 3 and 8 hours postdose, respectively.

Absorption

JANUMET XR

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

increased 62%, the C_{max} for metformin decreased by 9%, and the median T_{max} for metformin occurred 2 hours later relative to the fasted state.

Sitagliptin

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

Metformin hydrochloride

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an 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.

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 hydrochloride

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

Metabolism

Sitagliptin

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination.

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

limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Metformin hydrochloride

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

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 hydrochloride

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

Special Populations

Renal Impairment

Sitagliptin

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

Metformin hydrochloride

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

Hepatic Impairment

Sitagliptin

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

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

Metformin hydrochloride

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

Gender

Sitagliptin

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

Metformin hydrochloride

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

Geriatric

Sitagliptin

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

Metformin hydrochloride

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

Pediatric

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

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

Race

Sitagliptin

Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of available pharmacokinetic data, including subjects of white, Hispanic, black, Asian, and other racial groups.

Metformin hydrochloride

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

Body Mass Index (BMI)

Sitagliptin

Body mass index 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.

Drug Interactions

Sitagliptin and Metformin hydrochloride

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

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

Sitagliptin

In Vitro Assessment of Drug Interactions

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

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

In Vivo Assessment of Drug Interactions

Effect of Sitagliptin on Other Drugs

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

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

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

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

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

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

Effect of Other Drugs on Sitagliptin

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

Cyclosporine: A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of cyclosporine increased the AUC and C_{max} of sitagliptin by approximately 29% and 68%, respectively. These modest changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Metformin hydrochloride

[See Drug Interactions.]

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

JANUMET XR

No animal studies have been conducted with the combined products in JANUMET XR to evaluate carcinogenesis, mutagenesis or impairment of fertility. The following data are based on the findings in studies with sitagliptin and metformin individually.

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 combined liver adenoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results in exposures approximately 60 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 100 mg/day based on AUC comparisons. Liver tumors were not observed at 150 mg/kg, approximately 20 times the human exposure at the MRHD. A two-year carcinogenicity study was conducted in male and female mice given oral doses of sitagliptin of 50, 125, 250, and 500 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 500 mg/kg, approximately 70 times human exposure at the MRHD. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an *in vitro* cytogenetics assay in CHO, an *in vitro* rat hepatocyte DNA alkaline elution assay, and an *in vivo* micronucleus assay.

In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination (approximately 8 weeks total), and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, nondose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison).

Metformin hydrochloride

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 four times the maximum recommended human daily dose of 2000 mg 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.

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. 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.

CLINICAL STUDIES

There have been no clinical efficacy studies conducted with JANUMET XR; however, bioequivalence of JANUMET XR tablets with coadministered sitagliptin and extended-release metformin tablets was demonstrated for all tablet strengths.

Sitagliptin Add-on Therapy in Patients Not Adequately Controlled on Metformin Alone:

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin. Patients already on metformin (N = 431) at a dose of at least 1500 mg per day were randomized after completing a 2-week, single-blind placebo run-in period. Patients on metformin and another antihyperglycemic agent (N = 229) and patients not on any antihyperglycemic agents (off therapy for at least 8 weeks, N = 41) were randomized after a run-in period of approximately 10 weeks on metformin (at a dose of at least 1500 mg per day) in monotherapy. Patients were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

In combination with metformin, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin (Table 4). Rescue glycemic therapy was used in 5% of patients treated with sitagliptin 100 mg and 14% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table 4: Glycemic Parameters at Final Visit (24-Week Study) of Sitagliptin in Add-on Combination Therapy with Metformin†

	Sitagliptin 100 mg q.d. + Metformin	**Placebo + Metformin**
A1C (%)	**N = 453**	**N = 224**
Baseline (mean)	8.0	8.0
Change from baseline (adjusted mean‡)	-0.7	-0.0
Difference from placebo + metformin (adjusted mean‡) (95% CI)	-0.7§ (-0.8, -0.5)	
Patients (%) achieving A1C <7%	213 (47%)	41 (18%)
FPG (mg/dL)	**N = 454**	**N = 226**
Baseline (mean)	170	174
Change from baseline (adjusted mean‡)	-17	9
Difference from placebo + metformin (adjusted mean‡) (95% CI)	-25§ (-31, -20)	
2-hour PPG (mg/dL)	**N = 387**	**N = 182**

Baseline (mean)	275	272
Change from baseline (adjusted mean‡)	-62	-11
Difference from placebo + metformin (adjusted mean‡) (95% CI)	-51§ (-61, -41)	

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

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

§ *p<0.001 compared to placebo + metformin.*

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

Two hundred twenty nine (229) patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with glimepiride, with metformin. Patients entered a run-in treatment period on glimepiride (≥4 mg per day) in combination with metformin (≥1500 mg per day). After a dose-titration and dose-stable run-in period of up to 16 weeks and a 2-week placebo run-in period, patients with inadequate glycemic control (A1C 7.5% to 10.5%) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

Patients receiving sitagliptin with metformin and glimepiride had significant improvements in A1C and FPG compared to patients receiving placebo with metformin and glimepiride (Table 5), with mean reductions from baseline relative to placebo in A1C of -0.9% and in FPG of -21 mg/dL. Rescue therapy was used in 8% of patients treated with add-on sitagliptin 100 mg and 29% of patients treated with add-on placebo. The patients treated with add-on sitagliptin had a mean increase in body weight of 1.1 kg vs. add-on placebo (+0.4 kg vs. -0.7 kg). In addition, add-on sitagliptin resulted in an increased rate of hypoglycemia compared to add-on placebo. *[See Warnings and Precautions (5.9); Adverse Reactions (6.1).]*

Table 5: Glycemic Parameters at Final Visit (24-Week Study)

for Sitagliptin in Combination with Metformin and Glimepiride†

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

† Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy.

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

§ p<0.001 compared to placebo.

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

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin 100 mg once daily in combination with a stable dose of insulin. Approximately 75% of patients were also taking metformin. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin (≥1500 mg per day). Patients using short-acting insulins were excluded unless the

short-acting insulin was administered as part of a pre-mixed insulin. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized to the addition of either 100 mg of sitagliptin (N=229) or placebo (N=233), administered once daily. Patients were on a stable dose of insulin prior to enrollment with no changes in insulin dose permitted during the run-in period. Patients who failed to meet specific glycemic goals during the double-blind treatment period were to have uptitration of the background insulin dose as rescue therapy.

Among patients also receiving metformin, the median daily insulin (pre-mixed, intermediate or long acting) dose at baseline was 40 units in the sitagliptin-treated patients and 42 units in the placebo-treated patients. The median change from baseline in daily dose of insulin was zero for both groups at the end of the study. Patients receiving sitagliptin with metformin and insulin had significant improvements in A1C, FPG and 2-hour PPG compared to patients receiving placebo with metformin and insulin (Table 6). The adjusted mean change from baseline in body weight was -0.3 kg in patients receiving sitagliptin with metformin and insulin and -0.2 kg in patients receiving placebo with metformin and insulin. There was an increased rate of hypoglycemia in patients treated with sitagliptin. *[See Warnings and Precautions; Adverse Reactions]*

Table 6: Glycemic Parameters at Final Visit (24-Week Study)
for Sitagliptin as Add-on Combination Therapy with Metformin and Insulin†

	Sitagliptin 100 mg + Metformin + Insulin	Placebo + Metformin + Insulin
A1C (%)	**N = 223**	**N = 229**
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean‡, §)	-0.7	-0.1
Difference from placebo (adjusted mean‡) (95% CI)	-0.5‖ (-0.7, -0.4)	
Patients (%) achieving A1C (%) <7%	32 (14%)	12 (5%)
FPG (mg/dL)	**N = 225**	**N = 229**
Baseline (mean)	173	176
Change from baseline (adjusted mean‡)	-22	-4
Difference from placebo (adjusted mean‡) (95% CI)	-18‖ (-28, -8.4)	
2-hour PPG (mg/dL)	**N = 182**	**N = 189**
Baseline (mean)	281	281
Change from baseline (adjusted mean‡)	-39	1
Difference from placebo (adjusted mean‡) (95% CI)	-40‖ (-53, -28)	

† Intent-to-treat population using last observation on study prior to rescue therapy.

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

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

‖ p<0.001 compared to placebo.

In another 24-week, randomized, double-blind, placebo-controlled study designed to assess the insulin-sparing efficacy of sitagliptin as add-on combination therapy, 660 patients with inadequate glycemic control on insulin glargine with or without metformin (≥1500 mg per day) were randomized to the addition of either

100 mg of sitagliptin (N=330) or placebo (N=330), administered once daily while undergoing intensification of insulin therapy. Among patients taking metformin, baseline HbA_{1c} was 8.70% and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. Glycemic endpoints measured included HbA_{1c} and FPG.

Among patients taking metformin, at Week 24, the increase in daily insulin dose was 21% smaller in patients treated with sitagliptin (19 IU/day, N=285) than in patients treated with placebo (24 IU/day, N=283). The difference in insulin dose (-5 IU/day) was statistically significant (p=0.007). The reduction in HbA_{1c} for patients treated with sitagliptin, metformin, and insulin was -1.35% compared to -0.90% for patients treated with placebo, metformin, and insulin, a difference of -0.45% [95% CI: -0.62, -0.29]. The reduction in FPG for patients treated with sitagliptin, metformin, and insulin was -54.8 mg/dL compared to -43.0 mg/dL for patients treated with placebo, metformin, and insulin, a difference of -11.8 mg/dL [95% CI: -18.7, -4.9]. The incidence of hypoglycemia was 24.9% for patients treated with sitagliptin, metformin, and insulin and 37.8% for patients treated with placebo, metformin and insulin. The difference in incidence of hypoglycemia (-12.9%) was statistically significant (p<0.001).

TECOS Cardiovascular Safety Study

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

Over the course of the study, the overall estimated mean (SD) difference in HbA_{1c} between the sitagliptin and placebo groups was 0.29% (0.01), 95% CI (-0.32, -0.27); p<0.001. Patients in the sitagliptin group received fewer antihyperglycemic agents than did those in the placebo group (hazard ratio 0.72; 95% CI, 0.68 to 0.77; p≤0.001) and, among patients not on insulin at study entry, were less likely to start chronic insulin therapy (hazard ratio 0.70; 95% CI, 0.63 to 0.79; p<0.001.

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

After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalization for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes (Table 6).

Table 7

Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	SITAGLIPTIN 100 mg		Placebo		Hazard Ratio (95% CI)	p-value†
	N (%)	Incidence Rate per 100 Patient-Years*	N (%)	Incidence Rate per 100 Patient-Years*		
Analysis in the Per-Protocol Population						
Number of Patients	**7,257**		**7,266**			
Primary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina)	695 (9.6)	3.7	695 (9.6)	3.8	0.98 (0.88–1.09)	<0.001
Secondary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)	609 (8.4)	3.2	602 (8.3)	3.3	0.99 (0.89–1.11)	<0.001
Analysis in the Intention-to-Treat Population						
Number of Patients	**7,332**		**7,339**			
Primary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2	0.98 (0.89–1.08)	<0.001
Secondary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)	745 (10.2)	3.6	746 (10.2)	3.6	0.99 (0.89–1.10)	<0.001

Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89-1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81–1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79–1.19)	0.760
Hospitalization for unstable angina	116 (1.6)	0.5	129 (1.8)	0.6	0.90 (0.70–1.16)	0.419
Death from any cause	547 (7.5)	2.5	537 (7.3)	2.5	1.01 (0.90–1.14)	0.875
Hospitalization for heart failure‡	228 (3.1)	1.1	229 (3.1)	1.1	1.00 (0.83–1.20)	0.983

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

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

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

HOW SUPPLIED/STORAGE AND HANDLING

JANUMET XR 50/500 Bottle @ 28 tablets
Reg. No.: DKI1763500814A1
JANUMET XR 50/1000 Bottle @ 28 tablets
Reg. No.: DKI1763500814B1
JANUMET XR 100/1000 Bottle @ 28 tablets
Reg. No.: DKI1763500814C1

Manufactured by:
MSD International GmbH (Puerto Rico Branch) LLC, Puerto Rico.

Released by:
Merck Sharp & Dohme BV,
Haarlem, Netherlands

Storage

JANUMET XR
Store below 30°C. Once the bottle is opened, keep the container tightly closed and store in the original

package in a dry place. Shelf life: 24 months.

HARUS DENGAN RESEP DOKTER

Registered by:
PT Organon Pharma Indonesia Tbk
Pasuruan, Jawa Timur

Distributed by:
PT Merck Sharp & Dohme Indonesia
Jakarta, Indonesia

US-SPC, WPC-MK-0431A-T-062022
PI Version 5.0

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INFORMASI MENGENAI JANUMET™ XR UNTUK PASIEN

Bacalah lembar informasi ini dengan seksama sebelum Anda mulai menggunakan obat, meskipun Anda pernah menggunakan obat ini sebelumnya. Beberapa informasi dapat saja berubah.

Ingatlah bahwa dokter Anda meresepkan obat ini hanya untuk Anda. Jangan pernah memberikan obat Anda kepada orang lain.

Informasi penting apa yang harus diketahui tentang Janumet XR.

Efek samping serius yang mungkin muncul, termasuk:

1. Asidosis Laktat

Asidosis laktat adalah kejadian gawat medis yang dapat menyebabkan kematian dan harus dilakukan perawatan di rumah sakit. Asidosis laktat dapat menyebabkan penumpukan asam laktat dalam darah.

Hentikan penggunaan JANUMET XR dan segera hubungi dokter jika Anda mengalami gejala-gejala asidosis laktat berikut:

- Anda merasa sangat lemah dan letih.
- Anda mengalami nyeri otot yang tidak seperti biasanya.
- Anda mengalami masalah kesulitan bernapas.
- Anda mengalami nyeri perut dengan rasa mual, muntah, atau diare.
- Anda merasa kedinginan, terutama pada lengan dan kaki.
- Anda merasa pening atau pusing.
- Anda mengalami detak jantung yang melambat atau tidak teratur.
- Kondisi medis Anda tiba-tiba mengalami perubahan

Anda memiliki resiko tinggi mengalami asidosis laktat apabila Anda:

- Memiliki gangguan ginjal yang parah.
- Memiliki gangguan hati
- Memiliki gagal jantung kongestif yang mendapatkan perawatan obat-obatan.
- Mengkonsumsi alkohol berlebihan (sepanjang waktu atau peminum alkohol dalam jumlah banyak dalam waktu singkat).

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- Mengalami dehidrasi (kehilangan cairan tubuh dalam jumlah banyak). Ini dapat terjadi ketika Anda sakit dengan gejala demam, muntah atau diare. Dehidrasi juga dapat terjadi apabila Anda berkeringat secara berlebihan dengan beraktivitas atau berolahraga dan tidak minum air dengan cukup.
- Melakukan pemeriksaan sinar-x dengan penggunaan injeksi cairan pewarna atau agen pengontras.
- Melakukan operasi.
- Mengalami serangan jantung, infeksi parah, atau stroke.

2. Pankreatitis (radang pankreas) yang dapat menjadi parah dan mengakibatkan kematian

Apakah JANUMET XR?

JANUMET XR (sitagliptin phosphate/metformin hydrochloride extended-release, MSD) adalah tablet yang mengandung sitagliptin phosphate dan metformin hydrochloride lepas lambat sebagai zat aktif:

- JANUMET XR 50 mg sitagliptin phosphate /500 mg metformin hydrochloride lepas lambat
- JANUMET XR 50 mg sitagliptin phosphate /1000 mg metformin hydrochloride lepas lambat
- JANUMET XR 100 mg sitagliptin phosphate /1000 mg metformin hydrochloride lepas lambat

JANUMET XR diminum satu kali sehari.

Sebagai tambahan, JANUMET XR mengandung zat tambahan sebagai berikut:

- **Semua dosis JANUMET XR mengandung**: *povidone, hypromellose, colloidal silicon dioxide, sodium stearyl fumarate, propyl gallate, polyethylene glycol, and kaolin.* Penyalut tablet mengandung *hypromellose, hydroxypropyl cellulose, titanium dioxide, FD&C #2/Indigo Carmine Aluminum Lake* dan *carnauba wax.*
- **Kandungan tambahan pada JANUMET XR 50 mg/500 mg**: *microcrystalline cellulose.*
- **Kandungan tambahan pada JANUMET XR 50 mg/1000 mg**: *yellow iron oxide.*

JANUMET XR adalah tablet yang mengandung dua obat resep yakni sitagliptin fosfat (JANUVIA™) dan metformin, yang dapat menurunkan kadar gula dalam darah. Sitagliptin, adalah obat yang termasuk dalam kelas obat penghambat DPP-4 (penghambat dipeptidyl peptidase-4), dan metformin, adalah obat yang termasuk dalam kelas obat biguanide, keduanya bekerja bersamaan untuk mengontrol kadar gula dalam darah pada pasien dengan penyakit diabetes mellitus tipe-2. Diabetes tipe-2 disebut juga sebagai diabetes mellitus yang tidak-bergantung-insulin.

- JANUMET XR dapat menurunkan kadar gula dalam darah pada pasien diabetes tipe-2.
- JANUMET XR membantu meningkatkan kadar insulin setelah makan.
- JANUMET XR membantu tubuh untuk merespon lebih baik insulin yang dihasilkan sendiri.
- JANUMET XR dapat menyebabkan kadar gula yang terlalu rendah di dalam tubuh (hipoglikemia).

Didaftarkan oleh:

PT Organon Pharma Indonesia Tbk
Pasuruan, Jawa Timur

Didistribusikan oleh:

PT Merck Sharp & Dohme Indonesia
Jakarta, Indonesia

Produsen pembuat produk:

MSD International GmbH (Puerto Rico Branch) LLC,
Puerto Rico.

Mengapa dokter saya meresepkan JANUMET XR?

Dokter Anda meresepkan JANUMET XR, bersamaan dengan pengaturan makan dan olahraga, untuk membantu menurunkan kadar gula dalam darah Anda.

- JANUMET XR diindikasikan sebagai tambahan untuk diet dan olahraga untuk meningkatkan kontrol glikemik pada pasien dengan diabetes mellitus tipe 2 yang

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tidak terkontrol secara memadai pada metformin atau sitagliptin saja atau pada pasien yang telah dirawat dengan kombinasi sitagliptin dan metformin.

- JANUMET XR juga diindikasikan dalam kombinasi dengan sulfonylurea (yaitu terapi kombinasi rangkap tiga) sebagai tambahan untuk diet dan olahraga pada pasien dengan DM tipe 2 yang tidak terkontrol secara memadai dengan dua dari tiga agen: metformin, sitagliptin, atau sulfonylurea.
- JANUMET XR juga diindikasikan sebagai tambahan untuk insulin (yaitu, terapi kombinasi rangkap tiga) sebagai tambahan untuk diet dan olahraga untuk meningkatkan kontrol glikemik pada pasien ketika dosis stabil insulin dan metformin saja tidak memberikan kontrol glikemik yang memadai.

Ketika Janumet XR digunakan dalam kombinasi dengan sulfonylurea atau dengan insulin, dosis sulfonylurea atau insulin yang lebih rendah mungkin diperlukan untuk mengurangi risiko hipoglikemia.

Apakah Diabetes Mellitus tipe-2 itu?

Diabetes tipe 2 adalah suatu kondisi dimana tubuh Anda tidak menghasilkan cukup insulin, dan insulin yang diproduksi tubuh Anda tidak berfungsi sebagaimana mestinya. Tubuh Anda juga bisa menghasilkan terlalu banyak gula. Ketika ini terjadi, gula menumpuk di dalam darah. Ini dapat menyebabkan masalah medis yang serius.

Tujuan utama dalam mengobati diabetes adalah untuk menurunkan kadar gula dalam darah ke kadar normal. Menurunkan dan mengontrol kadar gula darah dapat mencegah atau menunda komplikasi akibat diabetes, seperti gangguan jantung, gangguan ginjal, kebutaan, dan amputasi.

Kadar gula darah dapat diturunkan melalui pengaturan makan dan olahraga, serta beberapa obat.

Apa yang harus saya tahu sebelum dan saat menggunakan JANUMET XR ?

Siapa yang tidak boleh menggunakan JANUMET XR?

Anda tidak boleh menggunakan JANUMET XR apabila Anda sedang mengalami kondisi-kondisi berikut:

- **Memiliki diabetes tipe-1.**
- **Memiliki gangguan ginjal yang parah.**

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- **Memiliki alergi terhadap sitagliptin (JANUVIA™), metformin hidroklorida, atau komponen lain pada JANUMET XR.** Lihat pada bagian **Apakah JANUMET XR?** untuk mengetahui daftar lengkap bahan-bahan pada JANUMET XR
- **Mempunyai kondisi yang disebut sebagai asidosis metabolik atau diabetes ketoasidosis** (terjadi peningkatan keton dalam darah atau urin)
- **Akan melakukan/menerima suntikan berupa pewarna atau agen pengontras untuk pemeriksaan sinar-x.**
  Konsultasikan pada dokter Anda ketika akan menghentikan penggunaan JANUMET XR dan ketika akan memulainya kembali

Apa yang harus saya katakan pada dokter sebelum dan saat menggunakan JANUMET XR?

Anda harus memberitahukan dokter Anda apabila Anda:

- Memiliki gangguan ginjal yang parah.
- Memiliki gangguan hati.
- Memiliki gangguan jantung yang disebut sebagai gagal jantung kongestif yang diobati dengan obat-obatan.
- Mengkonsumsi alkohol berlebihan (sepanjang waktu atau peminum alkohol dalam jumlah banyak dalam waktu singkat).
- Sedang hamil atau berencana untuk hamil.
- Sedang menyusui.
- Memiliki atau pernah memiliki reaksi alergi terhadap sitagliptin (JANUVIA), metformin, JANUMET XR.
- Sedang mengkonsumsi obat-obatan lain termasuk obat dengan resep, obat non resep, vitamin dan suplemen herbal. Simpan daftar obat yang Anda gunakan dan tunjukan kepada dokter dan apoteker Anda saat Anda menerima pengobatan baru.

Ketika menggunakan JANUMET XR

Kasus peradangan pada pankreas (pankreatitis) dilaporkan telah terjadi pada pasien yang menggunakan JANUMET XR. Pankreatitis dapat menjadi serius, berpotensi menjadi kondisi yang mengancam jiwa. Hentikan penggunaan JANUMET XR dan hubungi dokter Anda apabila Anda mengalami rasa sakit

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parah dibagian perut yang tidak hilang, dengan atau tanpa muntah, karena Anda kemungkinan mengalami pankreatitis.

Kasus reaksi kulit yang disebut *bullous pemphigoid* yang dapat memerlukan perawatan di rumah sakit telah dilaporkan pada pasien yang menerima JANUMET XR. Beritahu dokter Anda jika Anda mengalami lecet atau kerusakan kulit Anda (erosi). Dokter Anda mungkin menyuruh Anda berhenti mengkonsumsi JANUMET XR.

Penggunaan pada anak-anak

JANUMET dan JANUMET XR tidak efektif pada anak-anak dan remaja usia 10 hingga 17 tahun dengan diabetes tipe 2. JANUMET dan JANUMET XR belum diteliti pada anak di bawah 10 tahun.

Penggunaan pada lanjut usia

JANUMET XR harus digunakan dengan peringatan seiring dengan peningkatan usia. Kehati-hatian harus diperhatikan saat pemilihan dosis dan harus berdasarkan pengawasan yang cermat dan rutin pada fungsi ginjal.

Penggunaan pada wanita hamil dan menyusui

Wanita yang sedang hamil atau berencana hamil harus berkonsultasi dengan dokter terlebih dahulu sebelum menggunakan JANUMET XR. JANUMET XR tidak direkomendasikan penggunaannya selama kehamilan.

Belum diketahui apakah JANUMET XR dapat tersalurkan ke ASI. Anda sebaiknya tidak mengkonsumsi JANUMET XR apabila Anda sedang menyusui atau berencana untuk menyusui.

Dapatkah saya menggunakan JANUMET XR bersamaan dengan obat-obatan lain?

JANUMET XR dapat mempengaruhi cara kerja obat–obatan lain dan beberapa obat dapat mempengaruhi cara kerja JANUMET XR. Beritahukan kepada dokter Anda obat-obatan yang sedang Anda konsumsi termasuk obat-obat melalui resep, non resep, dan vitamin serta suplemen herbal.

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Dapatkah saya mengendarai kendaraan atau mengoperasikan mesin ketika saya menggunakan JANUMET XR?

Belum ada informasi tentang pengaruh JANUMET XR terhadap kemampuan dalam berkendara dan mengoperasikan mesin.

Bagaimana saya menggunakan JANUMET XR?

- Gunakan JANUMET XR secara tepat sesuai resep dokter. Dokter Anda akan memberitahukan jumlah JANUMET XR yang harus dikonsumsi.
- Dokter Anda dapat saja meningkatkan dosis Anda untuk mengontrol kadar gula darah Anda.
- Dokter Anda dapat saja meresepkan JANUMET XR bersamaan dengan sulfonylurea atau insulin (obat-obatan lain untuk menurunkan kadar gula darah).
- Konsumsilah JANUMET XR sehari sekali disarankan bersamaan dengan makanan pada malam hari untuk menurunkan resiko gangguan pencernaan.
- Jika Anda mengkonsumsi JANUMET XR, telan tablet JANUMET XR secara utuh. Jangan dikunyah, dipotong, atau dihancurkan. Beritahukan dokter Anda apabila Anda tidak bisa menelan tablet secara utuh.
- Anda dapat melihat sesuatu yang menyerupai tablet JANUMET XR pada feses Anda. Apabila Anda melihat tablet tersebut pada feses beberapa kali, beritahukan dokter Anda. Jangan menghentikan penggunaan JANUMET XR tanpa memberitahukan dokter Anda.
- Apabila tubuh Anda dalam keadaan stres, seperti demam, trauma (seperti kecelakaan mobil), infeksi atau operasi, jumlah obat diabetes yang dibutuhkan oleh Anda mungkin berubah. Beritahu dokter Anda segera apabila Anda mengalami salah satu masalah ini dan ikuti petunjuk dokter Anda.
- Cek gula darah Anda seperti yang dokter Anda minta.
- Tetap mengonsumsi diet dan program latihan yang ditetapkan ketika meminum JANUMET XR.
- Diskusikan dengan dokter Anda mengenai bagaimana cara mencegah, mengetahui, atau mengatasi gula darah rendah (hipoglikemia), gula darah tinggi (hiperglikemia), dan masalah lainnya yang berkaitan dengan diabetes yang Anda alami.
- Dokter Anda akan melakukan tes terhadap gula darah Anda secara rutin, termasuk kadar gula darah dan hemoglobin A_{1C} Anda.
- Dokter Anda akan melakukan tes darah untuk memastikan seberapa baik kerja ginjal Anda pada saat sebelum dan saat pengobatan dengan Janumet XR.

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- Lanjutkan penggunaan JANUMET XR sepanjang dokter Anda meresepkan agar Anda dapat terus mengontrol kadar gula darah Anda.

Anda dapat menghentikan penggunaan JANUMET XR dalam waktu singkat. Hubungilah dokter Anda untuk instruksi lebih lanjut apabila Anda:

- Memiliki kondisi yang mungkin berhubungan dengan dehidrasi (kehilangan cairan tubuh dalam jumlah banyak) seperti sakit dengan muntah yang parah, diare atau demam, atau ketika Anda meminum air lebih sedikit dari biasa.
- Berencana melakukan operasi.
- Akan melakukan/menerima suntikan berupa pewarna atau agen pengontras untuk pemeriksaan sinar-x.

Apa yang harus saya lakukan pada kejadian overdosis?

Jika Anda mengkonsumsi JANUMET XR secara berlebihan, segera hubungi dokter atau pusat pengawas kesehatan (*control poison)*.

Apa yang harus saya lakukan apabila saya melewatkan satu dosis?

Jika Anda melewatkan satu dosis, minumlah dosis tersebut segera setelah Anda mengingatnya. Apabila Anda tidak mengingatnya sampai waktu dosis berikutnya, lewati dosis tersebut dan kembalilah pada jadwal regular Anda. Jangan menggunakan dosis ganda JANUMET XR.

Apa saja efek yang tidak diinginkan yang dapat disebabkan oleh JANUMET XR?

Efek samping serius yang telah terjadi pada pasien yang menggunakan Janumet XR atau obat tunggal yang terkandung dalam janumet XR adalah sebagai berikut:

- Metformin, salah satu obat yang terkandung dalam Janumet XR dapat menyebabkan Asidosis Laktat. Lihat pada bagian **Informasi penting apa yang harus diketahui tentang Janumet XR.**
- **Peradangan pankreas**
- **Gula darah rendah (hipoglikemia). Risiko terjadinya hipoglikemia meningkat jika JANUMET XR** digunakan **bersama obat diabetes lainnya, seperti sulfonylurea.** Penurunan dosis sulfonylurea mungkin dibutuhkan ketika Anda meminum Janumet XR. Gejala terjadinya gula darah rendah adalah sebagai berikut: Sakit kepala, mengantuk, mudah marah, lapar, pusing, kebingungan,

berkeringat, merasa lelah, gelisah, jantung berdebar (detak jantung yang cepat).

- **Reaksi alergi, yang dapat menjadi serius, seperti, ruam, gatal-gatal, pembengkakan pada wajah, bibir, lidah, dan tenggorokan yang dapat menimbulkan kesulitan bernafas atau menelan. Jika Anda mengalami reaksi alergi, hentikan penggunaan JANUMET XR dan segera hubungi dokter. Dokter Anda mungkin akan meresepkan obat untuk mengatasi reaksi alergi dan obat lain untuk diabetes Anda.**
- Gangguan ginjal (beberapa membutuhkan dialisis)

Efek samping yang umum yang dapat terjadi pada penggunaan metformin sendiri adalah diare, mual/muntah, kembung, kelelahan, gangguan pencernaan, rasa tidak nyaman pada perut, dan sakit kepala. Diare dan mual/muntah diperlihatkan pada pasien yang menggunakan produk metformin lepas lambat.

Efek samping yang umum yang dapat terjadi pada penggunaan sitagliptin sendiri adalah hidung mampet atau berair serta sakit tenggorokan, infeksi saluran pernafasan atas, serta sakit kepala.

Efek samping yang diperlihatkan pada uji klinis menggunakan kombinasi sitagliptin dan metformin (obat yang terkandung pada JANUMET XR) secara umum menyerupai efek samping pada penggunaan tunggal metformin. Penggunaan JANUMET XR bersama dengan makanan dapat membantu menurunkan efek samping pada perut. Akan tetapi, apabila Anda mengalami gangguan perut yang tidak biasa atau tidak terduga, konsultasikan pada dokter Anda. Gangguan perut yang dimulai lama setelah penggunaan obat berlangsung dapat menandakan masalah serius.

Beberapa efek samping tambahan telah dilaporkan pada penggunaan umum JANUMET XR, atau sitagliptin, salah satu obat yang terkandung pada JANUMET XR. Efek samping tersebut telah dilaporkan ketika JANUMET XR, atau sitagliptin digunakan sendiri atau bersamaan dengan obat diabetes lain:

- Konstipasi.
- Muntah.
- Nyeri sendi.
- Nyeri otot.
- Nyeri lengan atau kaki.

- Nyeri punggung.
- Gatal-gatal.
- Lecet.

Efek samping lain yang tidak disebutkan di atas dapat muncul pada beberapa pasien.

Beritahu dokter atau apoteker jika Anda mengalami efek samping yang tidak biasa, atau jika efek samping yang telah diketahui tidak membaik atau memburuk.

Bagaimana saya dapat mengetahui lebih jauh mengenai JANUMET XR dan diabetes?

Anda dapat memperoleh informasi lebih lanjut melalui dokter Anda atau apoteker, yang memiliki informasi lebih detail.

Berapa lama saya harus menyimpan obat saya?

Jangan gunakan obat ini setelah tanggal pada keterangan setelah kata Exp. Date pada kemasan.

Bagaimana saya harus menyimpan JANUMET XR?

Simpan di bawah suhu 30°C. Setelah botol dibuka, simpan obat dalam botol dan tutup rapat kembali botol selama penyimpanan di tempat yang kering.

Jauhkan JANUMET XR dan semua obat-obatan dari jangkauan anak-anak.

HARUS DENGAN RESEP DOKTER

JANUMET XR 50/500 Botol @ 28 tablet
Reg. No.: DKI1763500814A1
JANUMET XR 50/1000 Botol @ 28 tablet
Reg. No.: DKI1763500814B1
JANUMET XR 100/1000 Botol @ 28 tablet
Reg. No.: DKI1763500814C1

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