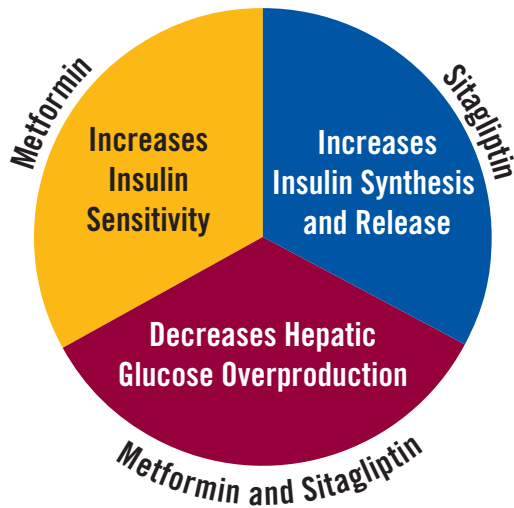


# JANUMET COMBINES SITAGLIPTIN, A DPP-4 INHIBITOR, WITH METFORMIN TO HELP IMPROVE GLYCEMIC CONTROL<sup>1-3</sup>

## Sitagliptin + metformin targets 3 core defects of diabetes

- JANUMET works in a glucose-dependent manner



### Metformin: Increases insulin sensitivity

- Metformin increases glucose uptake and utilization (liver > muscle and fat)
  - Increases glycogen synthesis<sup>1</sup>
  - Increases glucose uptake in liver<sup>2</sup>
  - Increases insulin sensitivity (liver > muscle and fat)<sup>1,2</sup>

### Sitagliptin: Increases insulin synthesis and release

- Sitagliptin increases active incretins, which stimulate synthesis and release of insulin from beta cells
  - Works in a glucose-dependent manner

### Metformin and sitagliptin: Decreases hepatic glucose overproduction

- Metformin reduces glucose production in the liver (gluconeogenesis) and diminishes the breakdown of glycogen into glucose (glycogenolysis)<sup>2,3</sup>
- Sitagliptin improves the ability of alpha cells to suppress glucagon secretion (by enhancing active incretin levels), which results in reduced glycogen breakdown and glucose synthesis
- Sitagliptin increases insulin synthesis and release from pancreatic beta cells, which helps reduce hepatic glucose overproduction<sup>1</sup>

DPP-4=dipeptidyl peptidase-4.

JANUMET is indicated, as an adjunct to diet and exercise, to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.

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

JANUMET has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while taking JANUMET.

## Selected Important Risk Information

### WARNING: LACTIC ACIDOSIS

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

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

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

If acidosis is suspected, JANUMET should be discontinued and the patient hospitalized immediately [see Warnings and Precautions].

JANUMET is contraindicated in patients with renal disease or renal dysfunction (serum creatinine levels  $\geq 1.5$  mg/dL in males and  $\geq 1.4$  mg/dL in females) or abnormal creatinine clearance; acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma; or history of a serious hypersensitivity reaction to JANUMET or sitagliptin (one of the components of JANUMET), such as anaphylaxis or angioedema.

Temporarily discontinue JANUMET 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. Avoid use in patients with hepatic disease. Temporarily discontinue for intercurrent serious conditions, infection, or surgery.

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis.

Measure renal function before initiation of therapy with JANUMET and periodically thereafter. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and JANUMET discontinued if evidence of renal impairment is present.

*(Selected Important Risk Information continues on page 2.)*

Before prescribing JANUMET, please read the accompanying Prescribing Information, including the Boxed Warning about lactic acidosis.

  
(sitagliptin/metformin HCl)  
tablets

# JANUMET TARGETS 3 CORE DEFECTS OF DIABETES FOR IMPROVED GLYCEMIC CONTROL<sup>1-3</sup>

## Selected Important Risk Information (*continued*)

When lactic acidosis occurs, it is fatal in approximately 50% of cases. The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications.

Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients  $\geq 80$  years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis.

There have been postmarketing reports of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUMET. After initiating JANUMET, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue JANUMET and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while taking JANUMET.

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

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, JANUMET should be temporarily discontinued at the time of or before the procedure, withheld for 48 hours subsequent to the procedure, and reinstated only after renal function has been re-evaluated and found to be normal.

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

### Use With Medications Known to Cause Hypoglycemia

#### *Sitagliptin*

When sitagliptin was used in combination with a sulfonylurea or insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or insulin. Therefore, patients also receiving insulin or an insulin secretagogue (eg, sulfonylurea) may require a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.

**Before prescribing JANUMET, please read the accompanying Prescribing Information, including the Boxed Warning about lactic acidosis.**

**References:** 1. Bailey CJ, Turner RC. Metformin. *N Engl J Med.* 1996;334(9):574-579. 2. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. *Ann Intern Med.* 2002;137(1):25-33. 3. Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. *Drugs.* 2005;65(3):385-411.

The incidence (and rate) of hypoglycemia based on all reports of symptomatic hypoglycemia were: 16.4% (0.82 episodes/patient-year) for sitagliptin 100 mg in combination with metformin and glimepiride, 0.9% (0.02 episodes/patient-year) for placebo in combination with metformin and glimepiride, 8.2% (0.61 episodes/patient-year) for placebo in combination with metformin and insulin, and 15.3% (0.98 episodes/patient-year) for sitagliptin in combination with metformin and insulin.

Adverse reactions with sitagliptin in combination with metformin and rosiglitazone through Week 18 were: upper respiratory tract infection (sitagliptin, 5.5%; placebo, 5.2%) and nasopharyngitis (6.1%, 4.1%). Through Week 54 they were: upper respiratory tract infection (sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%).

#### **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.

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUMET, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUMET, assess for other potential causes for the event, and institute alternative treatment for diabetes.

In clinical studies, the most common adverse reactions reported, regardless of investigator assessment of causality, in  $\geq 5\%$  of patients treated with either sitagliptin in combination with metformin or placebo were as follows: diarrhea (7.5% vs 4.0%), upper respiratory tract infection (6.2% vs 5.1%), and headache (5.9% vs 2.8%). In patients treated with sitagliptin in combination with metformin and sulfonylurea or placebo in combination with metformin and sulfonylurea: hypoglycemia (16.4% vs 0.9%) and headache (6.9% vs 2.7%). In patients treated with sitagliptin in combination with metformin and insulin or placebo in combination with metformin and insulin: hypoglycemia (15.3% vs 8.2%). Other adverse events with an incidence of  $\geq 5\%$  included nasopharyngitis for sitagliptin monotherapy and diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache for metformin therapy.



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