

**JANUET® XR 50 mg/500 mg  
Extended-release Tablets**

Each tablet contains:  
Sitagliptin (as phosphate salt) 50 mg  
Metformin hydrochloride (extended release) 500 mg

**JANUET® XR 50 mg/1000 mg  
Extended-release Tablets**

Each tablet contains:  
Sitagliptin (as phosphate salt) 50 mg  
Metformin Hydrochloride (extended release) 1000 mg

**JANUET® XR 100 mg/1000 mg  
Extended-release Tablets**

Each tablet contains:  
Sitagliptin (as phosphate salt) 100 mg  
Metformin Hydrochloride (extended release) 1000 mg

**WARNING: LACTIC ACIDOSIS**

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL [see *Warnings and Precautions (5.1)*].

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information [see *Dosage and Administration (2.2)*, *Contraindications (4)*, *Warnings and Precautions (5.1)*, *Drug Interactions (7)*, and *Use in Specific Populations (8.6, 8.7)*].

If metformin-associated lactic acidosis is suspected, immediately discontinue JANUET XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see *Warnings and Precautions (5.1)*].

**1 INDICATIONS AND USAGE**

JANUET® XR 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 extended-release is appropriate.

Important Limitations of Use

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

JANUET XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUET XR. [See *Warnings and Precautions (5.2)*.]

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Adults with normal renal function (estimated glomerular filtration rate [eGFR] $\geq$ 90 mL/min/1.73 m<sup>2</sup>)

The dose of JANUET 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 hydrochloride (HCl). Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

- In patients not currently treated with metformin, the recommended total daily starting dose of JANUET XR is 100 mg sitagliptin and 1000 mg metformin HCl extended-release. Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose.
- In patients already treated with metformin, the recommended total daily starting dose of JANUET XR is 100 mg sitagliptin and the previously prescribed dose of metformin.
- For patients taking metformin immediate-release 850 mg twice daily or 1000 mg twice daily, the recommended starting dose of JANUET XR is two 50 mg sitagliptin/1000 mg metformin HCl extended-release tablets taken together once daily.
- Maintain the same total daily dose of sitagliptin and metformin when changing between JANUET (sitagliptin and metformin HCl immediate-release) and JANUET XR. Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose.

JANUET XR should be administered with food to reduce the gastrointestinal side effects associated with the metformin component. JANUET XR should be given once daily with a meal preferably in the evening. JANUET XR should be swallowed whole. The tablets must not be split, crushed, or chewed before swallowing. There have been reports of incompletely dissolved JANUET 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 health care provider should assess adequacy of glycemic control.

The 100 mg sitagliptin/1000 mg metformin HCl extended-release tablet should be taken as a single tablet once daily. Patients using two JANUET XR tablets (such as two 50 mg sitagliptin/500 mg metformin HCl extended-release tablets or two 50 mg sitagliptin/1000 mg metformin HCl extended-release tablets) should take the two tablets together once daily.

*Patients treated with an insulin secretagogue or insulin*

*Coadministration of JANUET XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia [see Warnings and Precautions (5.9)].*

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

### 2.2 Recommendations for Use in Renal Impairment

An eGFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

Factors that may increase the risk of lactic acidosis [see Warnings and Precautions (5.1)] should be reviewed before considering initiation of metformin in patients with eGFR  $<$  60 mL/min/1.73 m<sup>2</sup>.

If no adequate strength of JANUET XR is available, individual monocomponents should be used instead of the fixed-dose combination.

<b>eGFR mL/min/1.73 m<sup>2</sup></b>	<b>Metformin</b>	<b>Sitagliptin</b>
60-89	Maximum daily dose is 2550 mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 100 mg.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 100 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 50 mg.
< 30	Metformin is contraindicated.	Maximum daily dose is 25 mg.

### 3 DOSAGE FORMS AND STRENGTHS

Tablets:

- sitagliptin 100 mg and metformin HCl 1000 mg extended-release tablets are blue, bi-convex oval, film-coated tablets with “81” debossed on one side.
- sitagliptin 50 mg and metformin HCl 500 mg extended-release tablets are light blue, bi-convex oval, film-coated tablets with “78” debossed on one side.
- sitagliptin 50 mg and metformin HCl 1000 mg extended-release tablets are light green, bi-convex oval, film-coated tablets with “80” debossed on one side.

### 4 CONTRAINDICATIONS

JANUET XR is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 11.
- Severe renal impairment (eGFR below 30 mL/min/1.73 m<sup>2</sup>) [see *Warnings and Precautions (5.1)*].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis.
- History of a serious hypersensitivity reaction to JANUET XR, sitagliptin, or metformin such as anaphylaxis or angioedema. [See *Warnings and Precautions (5.7)*; *Adverse Reactions (6.2)*.]

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Lactic Acidosis

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate/pyruvate ratio; metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of JANUET XR. In JANUET XR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis, and if these symptoms occur instruct them to discontinue JANUET XR and report these symptoms to their health care provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include [see *Dosage and Administration (2.2)*, *Clinical Pharmacology (12.3)*]:

- Before initiating JANUET XR, obtain an estimated glomerular filtration rate (eGFR).
- JANUET XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m<sup>2</sup>. Discontinue JANUET XR if the patient's eGFR later falls below 30 mL/min/1.73 m<sup>2</sup> [see *Contraindications (4)*].
- Initiation of JANUET XR is not recommended in patients with eGFR between 30 and 45 mL/min/1.73 m<sup>2</sup>.
- In patients taking JANUET XR whose eGFR later falls below 45 mL/min/1.73 m<sup>2</sup>, assess the benefit and risk of continuing therapy.
- Obtain an eGFR at least annually in all patients taking JANUET XR. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

#### *Drug Interactions*

The concomitant use of JANUET XR with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation [see *Drug Interactions (7)*]. Therefore, consider more frequent monitoring of patients.

#### *Age 65 or Greater*

The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients [see *Use in Specific Populations (8.5)*].

#### *Radiological Studies with Contrast*

Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop JANUET XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m<sup>2</sup>; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart JANUET XR if renal function is stable.

#### *Surgery and Other Procedures*

Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. JANUET XR should be temporarily discontinued while patients have restricted food and fluid intake.

#### *Hypoxic States*

Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue JANUET XR.

### *Excessive Alcohol Intake*

Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving JANUET XR.

### *Hepatic Impairment*

Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of JANUET XR in patients with clinical or laboratory evidence of hepatic disease.

## **5.2 Pancreatitis**

There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin with or without metformin. After initiation of JANUET XR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUET 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 JANUET XR.

## **5.3 Heart Failure**

An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of JANUET XR prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of JANUET XR.

## **5.4 Acute Renal Failure**

There have been postmarketing reports of worsening renal function in patients taking sitagliptin with or without metformin, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with JANUET 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 JANUET XR discontinued if evidence of renal impairment is present. JANUET XR is contraindicated in patients with severe renal impairment [*see Contraindications (4) and Warnings and Precautions (5.1)*].

## **5.5 Vitamin B<sub>12</sub> Deficiency**

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B<sub>12</sub> levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B<sub>12</sub> absorption from the B<sub>12</sub>-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B<sub>12</sub> supplementation. Certain individuals (those with inadequate vitamin B<sub>12</sub> or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B<sub>12</sub> levels. Measure hematologic parameters on an annual basis and vitamin B<sub>12</sub> measurements at 2- to 3-year intervals in patients on JANUET XR and manage any abnormalities [*see Adverse Reactions (6.1)*].

## **5.6 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues**

JANUET XR may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue (e.g., sulfonylurea) [*see Adverse Reactions (6)*]. A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with JANUET XR [*see Drug Interactions (7)*].

## 5.7 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUET XR. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUET XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. [See *Adverse Reactions* (6.2).]

Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUET XR.

## 5.8 Severe and Disabling Arthralgia

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

## 5.9 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 JANUET XR. If bullous pemphigoid is suspected, JANUET XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

## 5.10 Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

## 6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere in the labeling:

- Lactic Acidosis [see *Warnings and Precautions* (5.1)]
- Pancreatitis [see *Warnings and Precautions* (5.2)]
- Heart Failure [see *Warnings and Precautions* (5.3)]
- Acute Renal Failure [see *Warnings and Precautions* (5.4)]
- Vitamin B<sub>12</sub> Deficiency [see *Warnings and Precautions* (5.5)]
- Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues [see *Warnings and Precautions* (5.6)]
- Hypersensitivity Reactions [see *Warnings and Precautions* (5.7)]
- Severe and Disabling Arthralgia [see *Warnings and Precautions* (5.8)]
- Bullous Pemphigoid [see *Warnings and Precautions* (5.9)]

## 6.1 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 Immediate-Release Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise*

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

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

	Number of Patients (%)			
	Placebo	Sitagliptin 100 mg once daily	Metformin HCl Immediate-Release 500 mg or 1000 mg twice daily <sup>†</sup>	Sitagliptin 50 mg twice daily + Metformin HCl Immediate-Release 500 mg or 1000 mg twice daily <sup>†</sup>
	<b>N = 176</b>	<b>N = 179</b>	<b>N = 364<sup>†</sup></b>	<b>N = 372<sup>†</sup></b>
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.

<sup>†</sup> 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 Immediate-Release Alone*

In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily metformin immediate-release regimen, there were no adverse reactions reported regardless of investigator assessment of causality in  $\geq 5\%$  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 immediate-release, 1.9%; placebo and metformin immediate-release, 2.5%).

*Gastrointestinal Adverse Reactions*

The incidences of pre-selected gastrointestinal adverse experiences in patients treated with sitagliptin and metformin immediate-release were similar to those reported for patients treated with metformin immediate-release 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 Immediate-Release**

	Number of Patients (%)					
	Study of Sitagliptin and Metformin Immediate-Release in Patients Inadequately Controlled on Diet and Exercise				Study of Sitagliptin Add-on in Patients Inadequately Controlled on Metformin Immediate-Release Alone	
	Placebo	Sitagliptin 100 mg once daily	Metformin HCl Immediate-Release 500 mg or 1000 mg twice daily *	Sitagliptin 50 mg bid + Metformin HCl Immediate-Release 500 mg or 1000 mg twice daily *	Placebo and Metformin HCl Immediate-Release $\geq 1500$ mg daily	Sitagliptin 100 mg once daily and Metformin HCl Immediate-Release $\geq 1500$ mg daily
	<b>N = 176</b>	<b>N = 179</b>	<b>N = 364</b>	<b>N = 372</b>	<b>N = 237</b>	<b>N = 464</b>
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 <sup>†</sup>	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.

<sup>†</sup> Abdominal discomfort was included in the analysis of abdominal pain in the study of initial therapy.

### *Sitagliptin in Combination with Metformin Immediate-Release 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 immediate-release and glimepiride (sitagliptin, N=116; placebo, N=113), the adverse reactions reported regardless of investigator assessment of causality in  $\geq 5\%$  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 Immediate-Release and Rosiglitazone*

In a placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin immediate-release and rosiglitazone (sitagliptin, N=181; placebo, N=97), the adverse reactions reported regardless of investigator assessment of causality through Week 18 in  $\geq 5\%$  of patients treated with sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (sitagliptin, 5.5%; placebo, 5.2%) and nasopharyngitis (6.1%, 4.1%). Through Week 54, the adverse reactions reported regardless of investigator assessment of causality in  $\geq 5\%$  of patients treated with sitagliptin and more commonly than in patients treated with placebo 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%).

### *Sitagliptin in Combination with Metformin Immediate-Release 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 immediate-release and insulin (sitagliptin, N=229; placebo, N=233), the only adverse reaction reported regardless of investigator assessment of causality in  $\geq 5\%$  of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycemia (Table 3).

### *Hypoglycemia*

In the above studies (N=5), 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  $\leq 70$  mg/dL. When the combination of sitagliptin and metformin immediate-release was coadministered with a sulfonylurea or with insulin, the percentage of patients reporting at least one adverse reaction of hypoglycemia was higher than that observed with placebo and metformin immediate-release coadministered with a sulfonylurea or with insulin (Table 3).

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

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

<sup>†</sup> 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 immediate-release alone, and 1.6% in patients given sitagliptin in combination with metformin immediate-release. In patients with type 2 diabetes inadequately controlled on metformin immediate-release 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.

In the study of sitagliptin and add-on combination therapy with metformin immediate-release and rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on sitagliptin and 0.0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on sitagliptin and 1.0% in patients given add-on placebo.

In an additional 30-week placebo-controlled study of patients with type 2 diabetes inadequately controlled with metformin comparing the maintenance of sitagliptin 100 mg versus withdrawal of sitagliptin when initiating basal insulin therapy, the event rate and incidence of documented symptomatic hypoglycemia (blood glucose measurement  $\leq 70$  mg/dL) did not differ between the sitagliptin and placebo groups.

#### *Vital Signs and Electrocardiograms*

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

#### *Pancreatitis*

In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control).

#### *Sitagliptin*

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

#### *Metformin Extended-Release*

In a 24-week clinical trial in which extended-release metformin or placebo was added to glyburide therapy, the most common ( $>5\%$  and greater than placebo) adverse reactions in the combined treatment group were hypoglycemia (13.7% vs. 4.9%), diarrhea (12.5% vs. 5.6%), and nausea (6.7% vs. 4.2%).

#### *Laboratory Tests*

##### *Sitagliptin*

The incidence of laboratory adverse reactions was similar in patients treated with sitagliptin and metformin immediate-release (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*

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B<sub>12</sub> levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B<sub>12</sub> absorption from the B<sub>12</sub>-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B<sub>12</sub> supplementation.

## 6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of sitagliptin with metformin, sitagliptin, or metformin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome; upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis [see *Indications and Usage (1)*]; worsening renal function, including acute renal failure (sometimes requiring dialysis) and tubulointerstitial nephritis; severe and disabling arthralgia; bullous pemphigoid; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; mouth ulceration; stomatitis; cholestatic, hepatocellular, and mixed hepatocellular liver injury; rhabdomyolysis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

## 7 DRUG INTERACTIONS

Table 4 presents clinically significant drug interactions with JANUET XR:

<b>Table 4: Clinically Significant Drug Interactions with JANUET XR</b>	
<b>Carbonic Anhydrase Inhibitors</b>	
<i>Clinical Impact:</i>	Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with JANUET XR may increase the risk for lactic acidosis.
<i>Intervention:</i>	Consider more frequent monitoring of these patients.
<i>Examples:</i>	Topiramate, zonisamide, acetazolamide or dichlorphenamide.
<b>Drugs that Reduce Metformin Clearance</b>	
<i>Clinical Impact:</i>	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 [OCT <sub>2</sub> ] / multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see <i>Clinical Pharmacology (12.3)</i> ].
<i>Intervention:</i>	Consider the benefits and risks of concomitant use with JANUET XR.
<i>Examples:</i>	Ranolazine, vandetanib, dolutegravir, and cimetidine.
<b>Alcohol</b>	
<i>Clinical Impact:</i>	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
<i>Intervention:</i>	Warn patients against alcohol intake while receiving JANUET XR.
<b>Insulin Secretagogues or Insulin</b>	
<i>Clinical Impact:</i>	Coadministration of JANUET XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia.
<i>Intervention:</i>	Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.
<b>Drugs Affecting Glycemic Control</b>	
<i>Clinical Impact:</i>	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.
<i>Intervention:</i>	When such drugs are administered to a patient receiving JANUET XR,

	observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving JANUET XR, observe the patient closely for hypoglycemia.
<i>Examples:</i>	Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

The limited available data with JANUET XR in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk [see *Data*]. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*]. No adverse developmental effects were observed when sitagliptin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 30-times and 20-times, respectively, the 100 mg clinical dose, based on AUC. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during organogenesis at doses up to 2- and 6-times, respectively, a 2000 mg clinical dose, based on body surface area [see *Data*].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a Hemoglobin A1c >7% and has been reported to be as high as 20-25% in women with a Hemoglobin A1c >10%.

#### Clinical Considerations

##### *Disease-Associated Maternal and/or Embryo/Fetal Risk*

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

#### Data

##### *Human Data*

Published data from post-marketing studies do not report a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and inconsistent comparator groups.

##### *Animal Data*

##### *Sitagliptin and Metformin*

No animal reproduction studies were conducted with the coadministration of sitagliptin and metformin.

##### *Sitagliptin*

In embryo-fetal development studies, sitagliptin administered to pregnant rats and rabbits during organogenesis (gestation day 6 to 20) did not adversely affect developmental outcomes at oral doses up to 250 mg/kg (30-times the 100 mg clinical dose) and 125 mg/kg (20-times the 100 mg clinical dose), respectively, based on AUC. Higher doses in rats associated with maternal toxicity increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100-times the clinical dose, based on AUC. Placental transfer of sitagliptin was observed in pregnant rats and rabbits.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 caused no functional or behavioral toxicity in offspring of rats at doses up to 1000 mg/kg.

## *Metformin*

Metformin did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2- and 6-times a 2000 mg clinical dose based on body surface area (mg/m<sup>2</sup>) for rats and rabbits, respectively.

## **8.2 Lactation**

### Risk Summary

There is no information regarding the presence of JANUET XR in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk [see *Data*]. There are no reports of adverse effects on breastfed infants exposed to metformin. There is no information on the effects of metformin on milk production. Sitagliptin is present in rat milk and therefore possibly present in human milk [see *Data*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JANUET XR and any potential adverse effects on the breastfed infant from JANUET XR or from the underlying maternal condition.

### Data

#### *Sitagliptin*

Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1.

#### *Metformin*

Published clinical lactation studies report that metformin is present in human milk, which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

## **8.3 Females and Males of Reproductive Potential**

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

## **8.4 Pediatric Use**

JANUET XR is not indicated for children and adolescents under 18 years old.

## **8.5 Geriatric Use**

### *JANUET XR*

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy and the higher risk of lactic acidosis. Renal function should be assessed more frequently in elderly patients. [See *Contraindications (4)*; *Warnings and Precautions (5.1, 5.4)*; *Clinical Pharmacology (12.3)*.]

#### *Sitagliptin*

Of the total number of subjects (N=3884) in 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*

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.

## 8.6 Renal Impairment

### JANUET XR

The dose of the sitagliptin component should be limited to 50 mg once daily if eGFR falls below 45 mL/min/1.73 m<sup>2</sup>. JANUET XR is contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m<sup>2</sup>. [See *Dosage and Administration (2.2)*, *Contraindications (4)*, *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

#### Sitagliptin

Sitagliptin is excreted by the kidney, and sitagliptin exposure is increased in patients with renal impairment. [See *Clinical Pharmacology (12.3)*].

#### Metformin

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment.

## 8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. JANUET XR is not recommended in patients with hepatic impairment. [See *Warnings and Precautions (5.1)*].

## 10 OVERDOSAGE

In the event of an overdose, it is reasonable to employ 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.

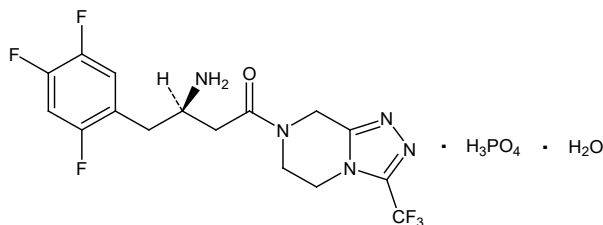
Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Warnings and Precautions (5.1)*]. 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.

## 11 DESCRIPTION

JANUET XR tablets for oral use contain two antihyperglycemic medications: sitagliptin and metformin extended-release.

#### Sitagliptin

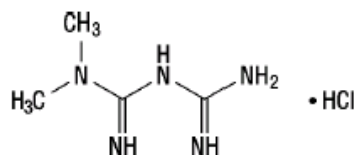
Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Sitagliptin phosphate monohydrate drug substance is used to manufacture JANUET XR. Sitagliptin phosphate monohydrate is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3- $\alpha$ ]pyrazine phosphate (1:1) monohydrate with an empirical formula of C<sub>16</sub>H<sub>15</sub>F<sub>6</sub>N<sub>5</sub>O•H<sub>3</sub>PO<sub>4</sub>•H<sub>2</sub>O and a molecular weight of 523.32. The structural formula is:



Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

### Metformin

Metformin HCl (*N,N*-dimethylimidodicarbonimidic diamide HCl) is a white to off-white crystalline compound with a molecular formula of  $C_4H_{11}N_5 \cdot HCl$  and a molecular weight of 165.63. Metformin HCl is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The  $pK_a$  of metformin HCl is 12.4. The pH of a 1% aqueous solution of metformin HCl is 6.68. The structural formula is as shown:



### JANUET XR

JANUET XR is available as film-coated tablets containing:

- 64.25 mg sitagliptin monohydrate equivalent to 50 mg sitagliptin and 500 mg metformin HCl (JANUET XR 50 mg/500 mg).
- 64.25 mg sitagliptin monohydrate equivalent to 50 mg sitagliptin and 1000 mg metformin HCl (JANUET XR 50 mg/1000 mg).
- 128.5 mg sitagliptin monohydrate equivalent to 100 mg sitagliptin and 1000 mg metformin HCl (JANUET XR 100 mg/1000 mg).

All doses of JANUET XR contain the following inactive ingredients: hypromellose, povidone, sodium stearyl fumarate, kaolin, polyethylene glycol, colloidal silicon dioxide, and propyl gallate. The JANUET XR 50 mg/500 mg tablet contains the additional inactive ingredient microcrystalline cellulose. In addition, the film coating for all doses contains the following inactive ingredients: hypromellose, hydroxypropyl cellulose, titanium dioxide, FD&C #2/Indigo Carmine Aluminum Lake and carnauba wax. The JANUET XR 50 mg/1000 mg tablet film coating also contains the inactive ingredient iron oxide yellow.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

#### JANUET XR

JANUET XR tablets combine two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes mellitus: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin extended-release, a member of the biguanide class.

#### Sitagliptin

Sitagliptin is a DPP-4 inhibitor, which exerts 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*

Metformin is a biguanide that improves glycemic control in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

## **12.2 Pharmacodynamics**

### *Sitagliptin*

In patients with type 2 diabetes mellitus, 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.

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

### *Sitagliptin and Metformin Coadministration*

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Coadministration of sitagliptin and metformin 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 mellitus.

### *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 mellitus 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.

## **12.3 Pharmacokinetics**

### *JANUET XR*

After administration of two JANUET 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 is reached by Day 4 and 5, respectively.

### *Sitagliptin*

The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes mellitus. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52  $\mu\text{M}\cdot\text{hr}$ ,  $C_{\text{max}}$  was 950 nM, and apparent terminal half-life ( $t_{1/2}$ ) was 12.4 hours. Plasma AUC of sitagliptin increased in a dose-proportional manner and increased approximately 14% following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes mellitus.

### *Absorption*

### *JANUET XR*

After administration of JANUET XR tablets once daily, the median  $T_{max}$  value for sitagliptin and metformin at steady state is approximately 3 and 8 hours postdose, respectively. The median  $T_{max}$  value for sitagliptin and metformin after administration of a single tablet of JANUET is 3 and 3.5 hours postdose, respectively.

#### *Effect of Food*

After administration of JANUET 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 JANUET 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*

After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed with peak plasma concentrations (median  $T_{max}$ ) occurring 1 to 4 hours postdose. The absolute bioavailability of sitagliptin is approximately 87%.

#### *Effect of Food*

Coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.

#### *Metformin*

The absolute bioavailability of a metformin HCl 500-mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin HCl tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg (approximately 1.3 times the maximum recommended daily dosage), indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

#### *Effect of Food*

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 HCl 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*

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin HCl tablets 850 mg averaged  $654 \pm 358$  L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally  $<1$  mcg/mL.

#### *Elimination*

##### *Sitagliptin*

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



### *Metformin*

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.

### *Metabolism*

#### *Sitagliptin*

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

### *Metformin*

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Metabolism studies with extended-release metformin tablets have not been conducted.

### *Excretion*

#### *Sitagliptin*

Following administration of an oral [<sup>14</sup>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.

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 (P-gp), which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a P-gp inhibitor, did not reduce the renal clearance of sitagliptin.

### *Metformin*

Elimination of metformin occurs primarily via renal excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

### *Specific Populations*

#### *Patients with Renal Impairment*

#### JANUET XR

Studies characterizing the pharmacokinetics of sitagliptin and metformin after administration of JANUET XR in renally impaired patients have not been performed [see *Dosage and Administration (2.2)*].

#### *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 less than 45 mL/min/1.73 m<sup>2</sup>, and an approximately 4-fold increase was observed in patients with severe renal impairment including patients with end-stage renal disease (ESRD) on hemodialysis, as compared to normal healthy control subjects. [See *Dosage and Administration (2.2)*].

#### *Metformin*

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased [see *Contraindications (4), Warnings and Precautions (5.1)*].

## *Patients with Hepatic Impairment*

### JANUET XR

Studies characterizing the pharmacokinetics of sitagliptin and metformin after administration of JANUET XR in patients with hepatic impairment have not been performed.

#### *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) [see *Use in Specific Populations (8.7)*].

#### *Metformin*

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

### *Effects of Age, Body Mass Index (BMI), Gender, and Race*

#### *Sitagliptin*

Based on a population pharmacokinetic analysis or a composite analysis of available pharmacokinetic data, BMI, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of 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*

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.

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

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

### *Drug Interaction Studies*

#### *JANUET XR*

Coadministration of multiple doses of sitagliptin (50 mg) and metformin HCl (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 JANUET XR have not been performed; however, such studies have been conducted with the individual components of JANUET XR (sitagliptin and metformin extended-release).

#### *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-gp substrate, but does not inhibit P-gp 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

#### Effects of Sitagliptin on Other Drugs

In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, digoxin, warfarin, or an oral contraception (ethinyl estradiol and norethindrone) (Table 5), providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, P-gp, and organic cationic transporter (OCT).

**Table 5: Effect of Sitagliptin on Systemic Exposure of Coadministered Drugs**

Coadministered Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without sitagliptin) No Effect = 1.00		
				AUC <sup>†</sup>	C <sub>max</sub>
Digoxin	0.25 mg <sup>‡</sup> once daily for 10 days	100 mg <sup>‡</sup> once daily for 10 days	Digoxin	1.11 <sup>§</sup>	1.18
Glyburide	1.25 mg	200 mg <sup>‡</sup> once daily for 6 days	Glyburide	1.09	1.01
Simvastatin	20 mg	200 mg <sup>‡</sup> once daily for 5 days	Simvastatin	0.85 <sup>¶</sup>	0.80
			Simvastatin Acid	1.12 <sup>¶</sup>	1.06
Rosiglitazone	4 mg	200 mg <sup>‡</sup> once daily for 5 days	Rosiglitazone	0.98	0.99
Warfarin	30 mg single dose on day 5	200 mg <sup>‡</sup> once daily for 11 days	S(-) Warfarin	0.95	0.89
			R(+) Warfarin	0.99	0.89
Ethinyl estradiol and norethindrone	21 days once daily of 35 µg ethinyl estradiol with norethindrone 0.5 mg x 7 days, 0.75 mg x 7 days, 1.0 mg x 7 days	200 mg <sup>‡</sup> once daily for 21 days	Ethinyl estradiol	0.99	0.97
			Norethindrone	1.03	0.98
Metformin HCl	1000 mg <sup>‡</sup> twice daily for 14 days	50 mg <sup>‡</sup> twice daily for 7 days	Metformin	1.02 <sup>#</sup>	0.97

\* All doses administered as single dose unless otherwise specified.

† AUC is reported as AUC<sub>0-∞</sub> unless otherwise specified.

‡ Multiple dose.

§ AUC<sub>0-24hr</sub>.

¶ AUC<sub>0-last</sub>.

# AUC<sub>0-12hr</sub>.

#### Effects of Other Drugs on Sitagliptin

Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by coadministered medications (Table 6).

**Table 6: Effect of Coadministered Drugs on Systemic Exposure of Sitagliptin**

Coadministered Drug		Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
					AUC <sup>†</sup>	C <sub>max</sub>
Cyclosporine		600 mg once daily	100 mg once daily	Sitagliptin	1.29	1.68
Metformin HCl		1000 mg <sup>‡</sup> twice daily for 14 days	50 mg <sup>‡</sup> twice daily for 7 days	Sitagliptin	1.02 <sup>§</sup>	1.05

\* All doses administered as single dose unless otherwise specified.

† AUC is reported as AUC<sub>0-∞</sub> unless otherwise specified.

‡ Multiple dose.

§ AUC<sub>0-12hr</sub>.

*Metformin*

**Table 7: Effect of Metformin on Systemic Exposure of Coadministered Drugs**

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without metformin) No Effect = 1.00		
				AUC <sup>†</sup>	C <sub>max</sub>
Cimetidine	400 mg	850 mg	Cimetidine	0.95 <sup>†</sup>	1.01
Glyburide	5 mg	500 mg <sup>§</sup>	Glyburide	0.78 <sup>¶</sup>	0.63 <sup>¶</sup>
Furosemide	40 mg	850 mg	Furosemide	0.87 <sup>¶</sup>	0.69 <sup>¶</sup>
Nifedipine	10 mg	850 mg	Nifedipine	1.10 <sup>‡</sup>	1.08
Propranolol	40 mg	850 mg	Propranolol	1.01 <sup>‡</sup>	0.94
Ibuprofen	400 mg	850 mg	Ibuprofen	0.97 <sup>#</sup>	1.01 <sup>#</sup>

\* All doses administered as single dose unless otherwise specified

† AUC is reported as AUC<sub>0-∞</sub> unless otherwise specified

‡ AUC<sub>0-24hr</sub>

§ GLUMETZA (metformin HCl extended-release tablets) 500 mg

¶ Ratio of arithmetic means, p value of difference <0.05

# Ratio of arithmetic means

**Table 8: Effect of Coadministered Drugs on Systemic Exposure of Metformin**

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC <sup>†</sup>	C <sub>max</sub>
Glyburide	5 mg	500 mg <sup>‡</sup>	Metformin <sup>‡</sup>	0.98 <sup>§</sup>	0.99 <sup>§</sup>
Furosemide	40 mg	850 mg	Metformin	1.09 <sup>§</sup>	1.22 <sup>§</sup>
Nifedipine	10 mg	850 mg	Metformin	1.16	1.21
Propranolol	40 mg	850 mg	Metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	Metformin	1.05 <sup>§</sup>	1.07 <sup>§</sup>
<b>Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin. [See Warnings and Precautions (5.1) and Drug Interactions (7).]</b>					
Cimetidine	400 mg	850 mg	Metformin	1.40	1.61
<b>Carbonic anhydrase inhibitors may cause metabolic acidosis [See Warnings and Precautions (5.1) and Drug Interactions (7).]</b>					
Topiramate	100 mg <sup>¶</sup>	500 mg <sup>¶</sup>	Metformin	1.25 <sup>¶</sup>	1.17

\* All doses administered as single dose unless otherwise specified

† AUC is reported as AUC<sub>0-∞</sub> unless otherwise specified

‡ GLUMETZA (metformin HCl extended-release tablets) 500 mg

§ Ratio of arithmetic means

¶ Steady state 100 mg Topiramate every 12 hr + metformin HCl 500 mg every 12 hr. AUC = AUC<sub>0-12hr</sub>

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### JANUET XR

No animal studies have been conducted with the combined products in JANUET 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*

Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of 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 rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses up to 2000 mg applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and *in vivo* mouse micronucleus tests were negative. Fertility of male or female rats was not affected by metformin when administered at doses up to 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

## 14 CLINICAL STUDIES

The coadministration of sitagliptin and metformin immediate-release has been studied in patients with type 2 diabetes inadequately controlled on diet and exercise and in combination with other antidiabetic medications.

There have been no clinical efficacy or safety studies conducted with JANUET XR to characterize its effect on hemoglobin A1c (A1C) reduction. Bioequivalence of JANUET XR tablets with coadministered sitagliptin and extended-release metformin tablets has been demonstrated for all tablet strengths [see *Clinical Pharmacology* (12.3)].

## **Metformin Extended-Release Compared to Metformin Immediate-Release in Patients with Type 2 Diabetes**

In a multicenter, randomized, double-blind, active-controlled, dose-ranging, parallel group trial extended-release metformin HCl 1500 mg once daily, extended-release metformin HCl 1500 mg per day in divided doses (500 mg in the morning and 1000 mg in the evening), and extended-release metformin HCl 2000 mg once daily were compared to immediate-release metformin HCl 1500 mg per day in divided doses (500 mg in the morning and 1000 mg in the evening). This trial enrolled patients (n = 338) who were newly diagnosed with diabetes, patients treated only with diet and exercise, patients treated with a single anti-diabetic medication (sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglitinides), and patients (n = 368) receiving metformin HCl up to 1500 mg/day plus a sulfonylurea at a dose equal to or less than one-half the maximum dose. Patients who were enrolled on monotherapy or combination antidiabetic therapy underwent a 6-week washout. Patients randomized to extended-release metformin HCl began titration from 1000 mg/day up to their assigned treatment dose over 3 weeks. Patients randomized to immediate-release metformin HCl initiated 500 mg twice daily for 1 week followed by 500 mg with breakfast and 1000 mg with dinner for the second week. The 3-week treatment period was followed by an additional 21-week period at the randomized dose. For HbA1c and fasting plasma glucose, each of the extended-release metformin regimens was at least as effective as immediate-release metformin. Additionally, once daily dosing of extended-release metformin was as effective as twice daily dosing of the immediate-release metformin formulation.

## **Sitagliptin and Metformin Immediate-Release Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise**

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

Sitagliptin and metformin immediate-release coadministration provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin immediate-release alone, and to sitagliptin alone (Table 9, Figure 1). For patients not on an antihyperglycemic agent at study entry, mean reductions from baseline in A1C were: sitagliptin 100 mg once daily, -1.1%; metformin HCl immediate-release 500 mg bid, -1.1%; metformin HCl immediate-release 1000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin HCl immediate-release 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin HCl immediate-release 1000 mg bid, -1.9%; and for patients receiving placebo, -0.2%. Lipid effects were generally neutral. The decrease in body weight in the groups given sitagliptin in combination with metformin immediate-release was similar to that in the groups given metformin alone or placebo.

**Table 9: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin and Metformin Immediate-Release, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise\***

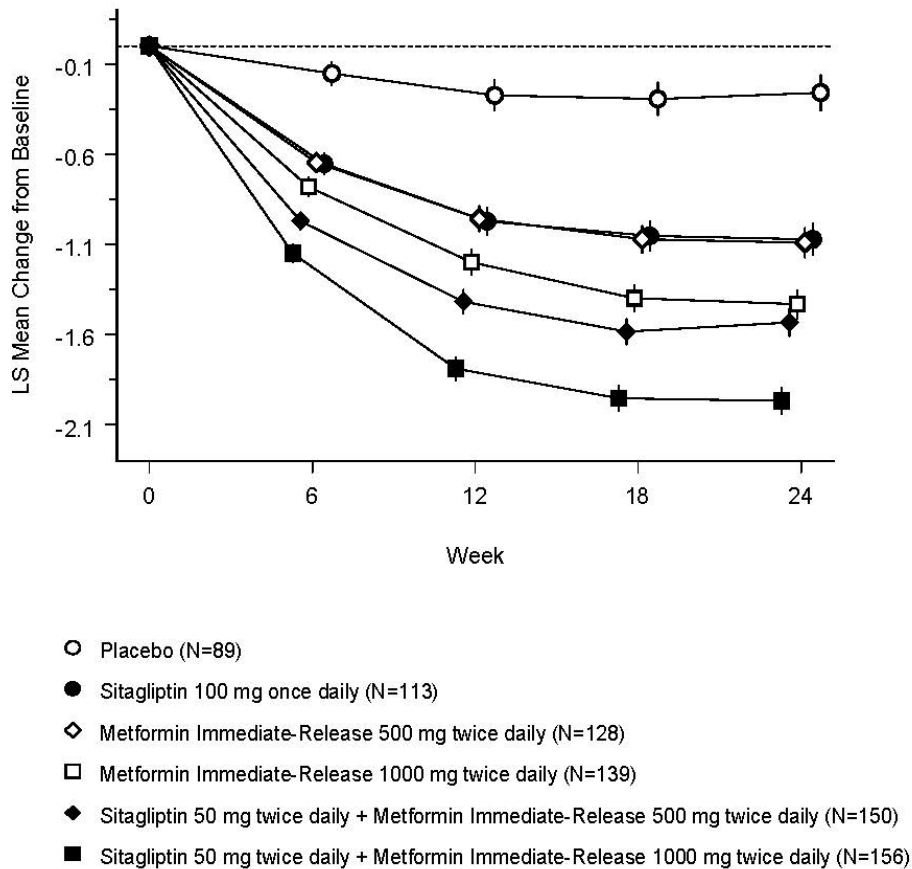
	Placebo	Sitagliptin 100 mg once daily	Metformin HCl Immediate- Release 500 mg twice daily	Metformin HCl Immediate- Release 1000 mg twice daily	Sitagliptin 50 mg bid + Metformin HCl Immediate- Release 500 mg twice daily	Sitagliptin 50 mg bid + Metformin HCl Immediate- Release 1000 mg twice daily
<b>A1C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

\* Intent-to-treat population using last observation on study prior to glyburide (glibenclamide) rescue therapy.

<sup>†</sup> Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

<sup>‡</sup> p<0.001 compared to placebo.

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



\* The Completers Population: least squares means adjusted for prior antihyperglycemic therapy and baseline value.

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

### **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Immediate-Release 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 immediate-release. Patients already on metformin HCl immediate-release (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 immediate-release 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 HCl immediate-release (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 immediate-release, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin immediate-release (Table 10). 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 10: Glycemic Parameters at Final Visit (24-Week Study) of Sitagliptin as Add-on Combination Therapy with Metformin Immediate-Release\***

	<b>Sitagliptin 100 mg once daily + Metformin Immediate-Release</b>	<b>Placebo + Metformin Immediate-Release</b>
<b>A1C (%)</b>	<b>N = 453</b>	<b>N = 224</b>
Baseline (mean)	8.0	8.0
Change from baseline (adjusted mean <sup>†</sup> )	-0.7	-0.0
Difference from placebo + metformin immediate-release (adjusted mean <sup>†</sup> ) (95% CI)	-0.7 <sup>‡</sup> (-0.8, -0.5)	
Patients (%) achieving A1C <7%	213 (47%)	41 (18%)
<b>FPG (mg/dL)</b>	<b>N = 454</b>	<b>N = 226</b>
Baseline (mean)	170	174
Change from baseline (adjusted mean <sup>†</sup> )	-17	9
Difference from placebo + metformin immediate-release (adjusted mean <sup>†</sup> ) (95% CI)	-25 <sup>‡</sup> (-31, -20)	
<b>2-hour PPG (mg/dL)</b>	<b>N = 387</b>	<b>N = 182</b>
Baseline (mean)	275	272
Change from baseline (adjusted mean <sup>†</sup> )	-62	-11
Difference from placebo + metformin immediate-release (adjusted mean <sup>†</sup> ) (95% CI)	-51 <sup>‡</sup> (-61, -41)	

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

<sup>†</sup> Least squares means adjusted for prior antihyperglycemic therapy and baseline value.

<sup>‡</sup> p<0.001 compared to placebo + metformin.

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

A total of 441 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with glimepiride, with or without metformin immediate-release. Patients entered a run-in treatment period on glimepiride (≥4 mg per day) alone or glimepiride in combination with metformin HCl immediate-release (≥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 immediate-release and glimepiride had significant improvements in A1C and FPG compared to patients receiving placebo with metformin immediate-release and glimepiride (Table 11), 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* (5.6); *Adverse Reactions* (6.1).]

**Table 11: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin in Combination with Metformin Immediate-Release and Glimepiride\***

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

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

<sup>†</sup> Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

<sup>‡</sup> p<0.001 compared to placebo.

### **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin Immediate-Release and Rosiglitazone**

A total of 278 patients with type 2 diabetes participated in a 54-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin immediate-release and rosiglitazone. Patients on dual therapy with metformin HCl immediate-release  $\geq 1500$  mg/day and rosiglitazone  $\geq 4$  mg/day or with metformin HCl immediate-release  $\geq 1500$  mg/day and pioglitazone  $\geq 30$  mg/day (switched to rosiglitazone  $\geq 4$  mg/day) entered a dose-stable run-in period of 6 weeks. Patients on other dual therapy were switched to metformin HCl immediate-release  $\geq 1500$  mg/day and rosiglitazone  $\geq 4$  mg/day in a dose titration/stabilization run-in period of up to 20 weeks in duration. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized 2:1 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 glipizide (or other sulfonylurea) rescue. The primary time point for evaluation of glycemic parameters was Week 18.

In combination with metformin immediate-release and rosiglitazone, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin immediate-release and rosiglitazone (Table 12) at Week 18. At Week 54, mean reduction in A1C was -1.0% for patients treated with sitagliptin and -0.3% for patients treated with placebo in an analysis based on the intent-to-treat population. Rescue therapy was used in 18% of patients treated with sitagliptin 100 mg and 40% of patients treated with placebo. There was no significant difference between sitagliptin and placebo in body weight change.

**Table 12: Glycemic Parameters at Week 18 for Sitagliptin in Add-on Combination Therapy with Metformin Immediate-Release and Rosiglitazone\***

	Week 18	
	Sitagliptin 100 mg + Metformin Immediate-Release + Rosiglitazone	Placebo + Metformin Immediate-Release + Rosiglitazone
<b>A1C (%)</b>	<b>N = 176</b>	<b>N = 93</b>
Baseline (mean)	8.8	8.7
Change from baseline (adjusted mean <sup>†</sup> )	-1.0	-0.4
Difference from placebo + rosiglitazone + metformin immediate-release (adjusted mean <sup>†</sup> ) (95% CI)	-0.7 <sup>‡</sup> (-0.9, -0.4)	
Patients (%) achieving A1C <7%	39 (22%)	9 (10%)
<b>FPG (mg/dL)</b>	<b>N = 179</b>	<b>N = 94</b>
Baseline (mean)	181	182
Change from baseline (adjusted mean <sup>†</sup> )	-30	-11
Difference from placebo + rosiglitazone + metformin immediate-release (adjusted mean <sup>†</sup> ) (95% CI)	-18 <sup>‡</sup> (-26, -10)	
<b>2-hour PPG (mg/dL)</b>	<b>N = 152</b>	<b>N = 80</b>
Baseline (mean)	256	248
Change from baseline (adjusted mean <sup>†</sup> )	-59	-21
Difference from placebo + rosiglitazone + metformin immediate-release (adjusted mean <sup>†</sup> ) (95% CI)	-39 <sup>‡</sup> (-51, -26)	

\* Intent-to-treat population using last observation on study prior to glipizide (or other sulfonylurea) rescue therapy.

<sup>†</sup> Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

<sup>‡</sup> p<0.001 compared to placebo + metformin + rosiglitazone.

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

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin as add-on to insulin therapy. Approximately 75% of patients were also taking metformin immediate-release. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin HCl immediate-release ( $\geq 1500$  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 up-titration of the background insulin dose as rescue therapy.

Among patients also receiving metformin immediate-release, 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 immediate-release and insulin had significant improvements in A1C, FPG and 2-hour PPG compared to patients receiving placebo with metformin immediate-release and insulin (Table 13). The adjusted mean change from baseline in body

weight was -0.3 kg in patients receiving sitagliptin with metformin immediate-release and insulin and -0.2 kg in patients receiving placebo with metformin immediate-release and insulin. There was an increased rate of hypoglycemia in patients treated with sitagliptin. [See *Warnings and Precautions (5.6)*; *Adverse Reactions (6.1)*.]

**Table 13: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin as Add-on Combination Therapy with Metformin Immediate-Release and Insulin\***

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

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

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

<sup>‡</sup> Treatment by insulin stratum interaction was not significant (p>0.10).

<sup>§</sup> p<0.001 compared to placebo.

### Maintenance of Sitagliptin During Initiation and Titration of Insulin Glargine

A total of 746 patients with type 2 diabetes (mean baseline HbA1C 8.8%, disease duration 10.8 years) participated in a 30-week, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of continuing sitagliptin during the initiation and uptitration of insulin glargine. Patients who were on a stable dose of metformin HCl (≥1500 mg/day) in combination with a DPP-4 inhibitor and/or sulfonylurea but with inadequate glycemic control (A1C 7.5% to 11%) were enrolled in the study. Those on metformin and sitagliptin (100 mg/day) directly entered the double-blind treatment period; those on another DPP-4 inhibitor and/or on a sulfonylurea entered a 4-8 week run-in period in which they were maintained on metformin and switched to sitagliptin (100 mg); other DPP-4 inhibitors and sulfonylureas were discontinued. At randomization patients were randomized either to continue sitagliptin or to discontinue sitagliptin and switch to a matching placebo. On the day of randomization, insulin glargine was initiated at a dose of 10 units subcutaneously in the evening. Patients were instructed to uptitrate their insulin dose in the evening based on fasting blood glucose measurements to achieve a target of 72-100 mg/dL.

At 30 weeks, the mean reduction in A1C was greater in the sitagliptin group than in the placebo group (Table 14). At the end of the trial, 27.3% of patients in the sitagliptin group and 27.3% in the placebo group had a fasting plasma glucose (FPG) in the target range; there was no significant difference in insulin dose between arms.

**Table 14: Change from Baseline in A1C and FPG at Week 30 in the Maintenance of Sitagliptin During Initiation and Titration of Insulin Glargine Study**

	<b>Sitagliptin 100 mg +Metformin + Insulin Glargine</b>	<b>Placebo +Metformin + Insulin Glargine</b>
<b>A1C (%)</b>	<b>N = 373<sup>†</sup></b>	<b>N = 370<sup>†</sup></b>
Baseline (mean)	8.8	8.8
Week 30 (mean)	6.9	7.3
Change from baseline (adjusted mean)*	-1.9	-1.4
Difference from placebo (adjusted mean) (95% CI)*	-0.4 (-0.6, -0.3) <sup>‡</sup>	
Patients (%) with A1C <7%	202 (54.2%)	131 (35.4%)
<b>FPG (mg/dL)</b>	<b>N = 373<sup>†</sup></b>	<b>N = 370<sup>†</sup></b>
Baseline (mean)	199	201
Week 30 (mean)	118	123
Change from baseline (adjusted mean)*	-81	-76

\* Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputation to model washout of the treatment effect using placebo data for all subjects having missing Week 30 data.

<sup>†</sup> N is the number of randomized and treated patients.

<sup>‡</sup> p<0.001 compared to placebo.

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

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

After 52 weeks, sitagliptin and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis (Table 15). These results were consistent with the per protocol analysis (Figure 2). A conclusion in favor of the non-inferiority of sitagliptin to glipizide may be limited to patients with baseline A1C comparable to those included in the study (over 70% of patients had baseline A1C <8% and over 90% had A1C <9%).

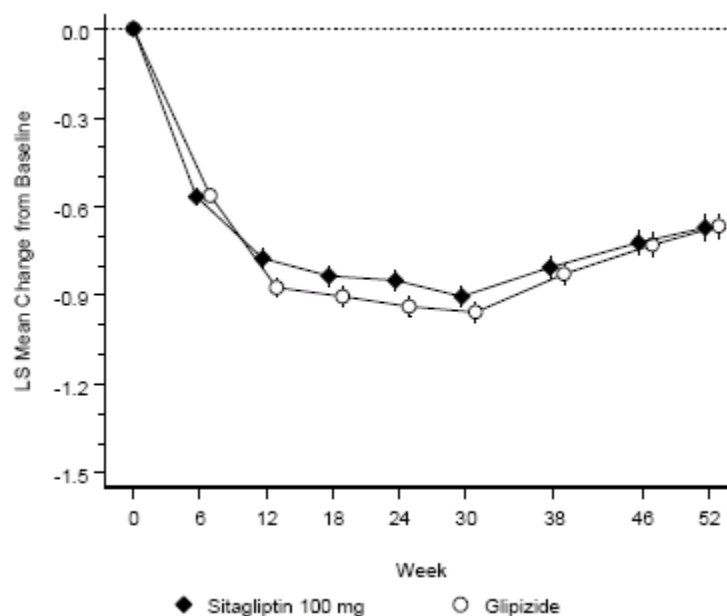
**Table 15: Glycemic Parameters in a 52-Week Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin Immediate-Release (Intent-to-Treat Population) \***

	Sitagliptin 100 mg + Metformin Immediate-Release	Glipizide + Metformin Immediate-Release
<b>A1C (%)</b>	<b>N = 576</b>	<b>N = 559</b>
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean <sup>†</sup> )	-0.5	-0.6
<b>FPG (mg/dL)</b>	<b>N = 583</b>	<b>N = 568</b>
Baseline (mean)	166	164
Change from baseline (adjusted mean <sup>†</sup> )	-8	-8

\* The intent-to-treat analysis used the patients' last observation in the study prior to discontinuation.

<sup>†</sup> Least squares means adjusted for prior antihyperglycemic therapy status and baseline A1C value.

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



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

The incidence of hypoglycemia in the sitagliptin group (4.9%) was significantly ( $p < 0.001$ ) lower than that in the glipizide group (32.0%). Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs. +1.1 kg).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets: JANUET XR, 50 mg/500 mg, are light blue, bi-convex oval, film-coated tablets with “78” debossed on one side. They are supplied as follows: unit-of-use bottles of 14, 60

Tablets: JANUET XR, 50 mg/1000 mg, are light green, bi-convex oval, film-coated tablets with “80” debossed on one side. They are supplied as follows: unit-of-use bottles of 14, 60

Tablets: JANUET XR, 100 mg/1000 mg, are blue, bi-convex oval, film-coated tablets with "81" debossed on one side. They are supplied as follows: unit-of-use bottles of 7, 30

Not all pack sizes may be marketed.

Do not store above 25°C. Store in a dry place and keep cap tightly closed.

The expiry date of the product is indicated on the packaging materials

Shelf life after first opening: can be used until end of expiry date.

**Marketing authorization holder and importer:** Merck Sharp & Dohme (Israel-1996) Company Ltd., 34 Ha'charash St., Hod-Hasharon.

**Drug registration no. listed in the official registry of the Ministry of Health:**

Januet XR 50/500 mg Tablets: 151.31.33932

Januet XR 50/1000 mg Tablets: 151.32.33933

Januet XR 100/1000 mg Tablets: 151.33.33934

Revised in September 2022 according to MOHs guidelines.