

## 1. NAME OF THE MEDICINAL PRODUCT

SITAGLIPTIN-METFORMIN SANDOZ FILM COATED TABLET 50MG/500MG

SITAGLIPTIN-METFORMIN SANDOZ FILM COATED TABLET 50MG/850MG

SITAGLIPTIN-METFORMIN SANDOZ FILM COATED TABLET 50MG/1000MG

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SITAGLIPTIN-METFORMIN SANDOZ FILM COATED TABLET 50MG/500MG contains sitagliptin (as phosphate monohydrate) 50 mg and metformin hydrochloride 500 mg.

Each SITAGLIPTIN-METFORMIN SANDOZ FILM COATED TABLET 50MG/850MG contains sitagliptin (as phosphate monohydrate) 50 mg and metformin hydrochloride 850 mg.

Each SITAGLIPTIN-METFORMIN SANDOZ FILM COATED TABLET 50MG/1000MG contains sitagliptin (as phosphate monohydrate) 50 mg and metformin hydrochloride 1000 mg.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film coated tablet.

SITAGLIPTIN-METFORMIN SANDOZ FILM COATED TABLET 50MG/500MG

Pink, oval, biconvex film coated tablet debossed with “SM01” on one side.

SITAGLIPTIN-METFORMIN SANDOZ FILM COATED TABLET 50MG/850MG

Light orange, oval, biconvex film coated tablet debossed with “SM02” on one side.

SITAGLIPTIN-METFORMIN SANDOZ FILM COATED TABLET 50MG/1000MG

Light red, oval, biconvex film coated tablet debossed with “SM03” on one side.

### **WARNING: LACTIC ACIDOSIS**

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

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

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

If acidosis is suspected, SITAGLIPTIN-METFORMIN SANDOZ should be discontinued and the patient hospitalized immediately (see section 4.4).

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

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

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

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

#### Important Limitations of Use

SITAGLIPTIN-METFORMIN SANDOZ should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

SITAGLIPTIN-METFORMIN SANDOZ 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 SITAGLIPTIN-METFORMIN SANDOZ (see section 4.4).

## **4.2 Posology and method of administration**

### Recommended Dosing

The dosage of antihyperglycemic therapy with SITAGLIPTIN-METFORMIN SANDOZ 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. Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

SITAGLIPTIN-METFORMIN SANDOZ should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin.

The starting dose of SITAGLIPTIN-METFORMIN SANDOZ should be based on the patient's current regimen. SITAGLIPTIN-METFORMIN SANDOZ should be given twice daily with meals. The following doses are available:

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

### *Patients inadequately controlled with diet and exercise alone*

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient with type 2 diabetes mellitus inadequately controlled with diet and exercise alone, the recommended starting dose is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily. Patients with inadequate glycemic control on this dose can be titrated up to 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily.

### *Patients inadequately controlled on metformin monotherapy*

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient inadequately controlled on metformin alone, the recommended starting dose of SITAGLIPTIN-METFORMIN SANDOZ should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken.

### *Patients inadequately controlled on sitagliptin monotherapy*

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient inadequately controlled on sitagliptin alone, the recommended starting dose of SITAGLIPTIN-METFORMIN SANDOZ is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily. Patients with inadequate control on this dose can be titrated up to 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily. Patients taking sitagliptin monotherapy dose-adjusted for renal impairment should not be switched to SITAGLIPTIN-METFORMIN SANDOZ (see section 4.3).

### *Patients switching from co-administration of sitagliptin and metformin*

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

*Patients inadequately controlled on dual combination therapy with any two of the following antihyperglycemic agents: sitagliptin, metformin or a sulfonylurea*

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate in this setting, the usual starting dose of SITAGLIPTIN-METFORMIN SANDOZ should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. Patients currently on or initiating a sulfonylurea may require lower sulfonylurea doses to reduce the risk of hypoglycemia (see section 4.4).

*For patients inadequately controlled on dual combination therapy with insulin and metformin*

The usual starting dose of SITAGLIPTIN-METFORMIN SANDOZ should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. Patients currently on or initiating insulin therapy may require lower doses of insulin to reduce the risk of hypoglycemia (see section 4.4).

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

*Recommendations for use in renal impairment*

Assess renal function prior to initiation of SITAGLIPTIN-METFORMIN SANDOZ and periodically thereafter.

SITAGLIPTIN-METFORMIN SANDOZ is contraindicated in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m<sup>2</sup>.

SITAGLIPTIN-METFORMIN SANDOZ is not recommended in patients with an eGFR  $\geq$  30 mL/min/1.73 m<sup>2</sup> and < 45 mL/min/1.73 m<sup>2</sup> because these patients require a lower dosage of sitagliptin than what is available in the fixed combination SITAGLIPTIN-METFORMIN SANDOZ product.

*Discontinuation for iodinated contrast imaging procedures*

Discontinue SITAGLIPTIN-METFORMIN SANDOZ at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR  $\geq$  30 to < 60 mL/min/1.73 m<sup>2</sup>; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart SITAGLIPTIN-METFORMIN SANDOZ if renal function is acceptable (see section 4.4).

*Pediatric Use*

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

The results do not support use of sitagliptin-metformin or sitagliptin-metformin XR in pediatric subjects (10 to 17 years old) with type 2 diabetes (see section 5.1).

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

Sitagliptin-metformin and sitagliptin-metformin XR have not been studied in pediatric patients under 10 years of age.

#### Geriatric Use

##### *SITAGLIPTIN-METFORMIN SANDOZ*

Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, SITAGLIPTIN-METFORMIN SANDOZ should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function (see sections 4.4 and 5.2).

#### *Sitagliptin*

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

#### *Metformin hydrochloride*

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

#### Method of administration

For oral administration.

SITAGLIPTIN-METFORMIN SANDOZ should be given twice daily with meals to reduce the gastrointestinal (GI) side effects due to metformin.

### **4.3 Contraindications**

SITAGLIPTIN-METFORMIN SANDOZ (sitagliptin and metformin HCl) is contraindicated in patients with:

- Severe renal impairment ( $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ ) (see section 4.4)
- Hypersensitivity to metformin hydrochloride
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin
- History of a serious hypersensitivity reaction to SITAGLIPTIN-METFORMIN SANDOZ or sitagliptin (one of the components of SITAGLIPTIN-METFORMIN SANDOZ), such as anaphylaxis or angioedema. [see sections 4.4 and 4.8]

### **4.4 Special warnings and precautions for use**

#### Lactic Acidosis

##### Metformin hydrochloride

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with SITAGLIPTIN-METFORMIN SANDOZ; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels ( $>5$

mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels  $>5$   $\mu\text{g/mL}$  are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications (see section 4.2). Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see section 4.4).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see section 4.4). Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug-related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling (see section 4.4).

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see sections 4.3 and 4.4).

### **Pancreatitis**

There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin-metformin. After initiation of SITAGLIPTIN-METFORMIN SANDOZ, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, SITAGLIPTIN-METFORMIN SANDOZ 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 SITAGLIPTIN-METFORMIN SANDOZ.

### **Impaired Hepatic Function**

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

### **Assessment of Renal Function**

Metformin and sitagliptin are known to be substantially excreted by the kidney.

#### **Metformin hydrochloride**

The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, SITAGLIPTIN-METFORMIN SANDOZ is contraindicated in severe renal impairment, patients with an eGFR < 30 mL/min/1.73 m<sup>2</sup> (see sections 4.2, 4.3 and 4.4). Before initiation of SITAGLIPTIN-METFORMIN SANDOZ and at least annually thereafter, renal function should be assessed. In patients in whom development of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and SITAGLIPTIN-METFORMIN SANDOZ discontinued if evidence of renal impairment is present.

#### **Sitagliptin**

Before initiation of therapy with SITAGLIPTIN-METFORMIN SANDOZ and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and SITAGLIPTIN-METFORMIN SANDOZ discontinued if evidence of renal impairment is present.

### **Vitamin B<sub>12</sub> Levels**

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. Measurement of hematologic parameters on an annual basis is advised in patients on SITAGLIPTIN-METFORMIN SANDOZ and any apparent abnormalities should be appropriately investigated and managed (see section 4.8).

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. In these patients, routine serum Vitamin B<sub>12</sub> measurements at two- to three-year intervals may be useful.

### **Alcohol Intake**

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

### **Surgical Procedures**

Use of SITAGLIPTIN-METFORMIN SANDOZ should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and

should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as acceptable (see section 4.2).

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

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

#### **Use with Medications Known to Cause Hypoglycemia**

##### **Sitagliptin**

As typical with other antihyperglycemic agents, hypoglycemia has been observed when sitagliptin was used in combination with insulin or a sulfonylurea (see section 4.8). Therefore, patients also receiving an insulin secretagogue (e.g., sulfonylurea) or insulin may require a lower dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia (see section 4.2).

##### **Metformin hydrochloride**

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking  $\beta$ -adrenergic blocking drugs.

#### **Concomitant Medications Affecting Renal Function or Metformin Disposition**

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see section 4.5), should be used with caution.

#### **Radiologic Studies with Intravascular Iodinated Contrast Materials**

Intravascular contrast studies with iodinated materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see section 4.3). Therefore, in patients with an eGFR  $\geq 30$  to  $< 60$  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, SITAGLIPTIN-METFORMIN SANDOZ should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be acceptable (see section 4.2).

#### **Hypoxic States**

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

#### **Loss of Control of Blood Glucose**

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to

withhold SITAGLIPTIN-METFORMIN SANDOZ and temporarily administer insulin. SITAGLIPTIN-METFORMIN SANDOZ may be reinstituted after the acute episode is resolved.

### **Hypersensitivity Reactions**

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of SITAGLIPTIN-METFORMIN SANDOZ. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue SITAGLIPTIN-METFORMIN SANDOZ, assess for other potential causes for the event, and institute alternative treatment for diabetes (see section 4.8).

### **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 SITAGLIPTIN-METFORMIN SANDOZ. If bullous pemphigoid is suspected, SITAGLIPTIN-METFORMIN SANDOZ should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

### **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.

### **Macrovascular Outcomes**

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

## **4.5 Interaction with other medicinal products and other forms of interaction**

### **Carbonic Anhydrase Inhibitors**

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with SITAGLIPTIN-METFORMIN SANDOZ, as the risk of lactic acidosis may increase.

### **Drugs that reduce metformin clearance**

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

### **The Use of Metformin with Other Drugs**

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs,



and isoniazid. When such drugs are administered to a patient receiving SITAGLIPTIN-METFORMIN SANDOZ the patient should be closely observed to maintain adequate glycemic control.

See also section 5.2.

#### **4.6 Pregnancy and lactation**

##### **Pregnancy**

##### **SITAGLIPTIN-METFORMIN SANDOZ**

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

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

##### **Sitagliptin**

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

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

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

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

##### **Metformin hydrochloride**

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

##### **Nursing Mothers**

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

#### **4.7 Effects on ability to drive and use machines**

Sitagliptin/metformin hydrochloride has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported with sitagliptin.

In addition, patients should be alerted to the risk of hypoglycaemia.

#### 4.8 Undesirable effects

##### Clinical Trials Experience

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

##### Sitagliptin and Metformin Co-administration 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 were co-administered to patients with type 2 diabetes inadequately controlled on diet and exercise.

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

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

<sup>†</sup> 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 Alone

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

##### Gastrointestinal Adverse Reactions

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

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

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

<sup>†</sup> 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 and Glimepiride

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

#### Sitagliptin in Combination with Metformin and Insulin

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

#### Hypoglycemia

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

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

<b>Add-On to Glimepiride + Metformin (24 weeks)</b>	<b>Sitagliptin 100 mg + Metformin + Glimepiride</b>	<b>Placebo + Metformin + 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 (24 weeks)</b>	<b>Sitagliptin 100 mg + Metformin + Insulin</b>	<b>Placebo + Metformin + 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)

<sup>†</sup> 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).

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

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

#### Vital Signs and Electrocardiograms

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

#### Pancreatitis

In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of non-adjudicated acute pancreatitis events was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control). See also *TECOS Cardiovascular Safety Study* below (see section 4.4).

#### Sitagliptin

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

#### Metformin hydrochloride

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

### TECOS Cardiovascular Safety Study

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

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

### Pediatric Population

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

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

### Laboratory Tests

#### Sitagliptin

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

#### Metformin hydrochloride

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B<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 (see section 4.4).

### Postmarketing Experience

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

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome (see section 4.4); upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see sections 4.1 and 4.4); worsening renal function, including acute renal failure (sometimes requiring dialysis) and tubulointerstitial nephritis; bullous pemphigoid (see sections 4.4); severe and disabling arthralgia (see sections 4.4); constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus.

#### **4.9 Overdose**

##### **Sitagliptin**

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Maximal mean increases in QTc of 8.0 msec were observed in one study at a dose of 800 mg sitagliptin, a mean effect that is not considered clinically important (see section 5.1). There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy as indicated by the patient's clinical status.

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

##### **Metformin hydrochloride**

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see section 4.4). 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.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs, ATC code: A10BD07

##### **Mechanism of Action**

##### **SITAGLIPTIN-METFORMIN SANDOZ**

SITAGLIPTIN-METFORMIN SANDOZ combines two antidiabetic medications with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

##### **Sitagliptin**

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

#### Metformin hydrochloride

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects [except in special circumstances (see section 4.4)] and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

#### **Pharmacodynamics**

##### Sitagliptin

##### General

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

##### Sitagliptin and Metformin hydrochloride Co-administration

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

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

##### Cardiac Electrophysiology

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

plasma concentrations were approximately 11 times higher than the peak concentrations following a 100-mg dose.

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

### **CLINICAL STUDIES**

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

None of the clinical efficacy studies in adults described below was conducted with sitagliptin-metformin.

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

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

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

	Placebo	Sitagliptin 100 mg once daily	Metformin 500 mg twice daily	Metformin 1000 mg twice daily	Sitagliptin 50 mg twice daily + Metformin 500 mg twice daily	Sitagliptin 50 mg twice daily + Metformin 1000 mg twice daily
<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>



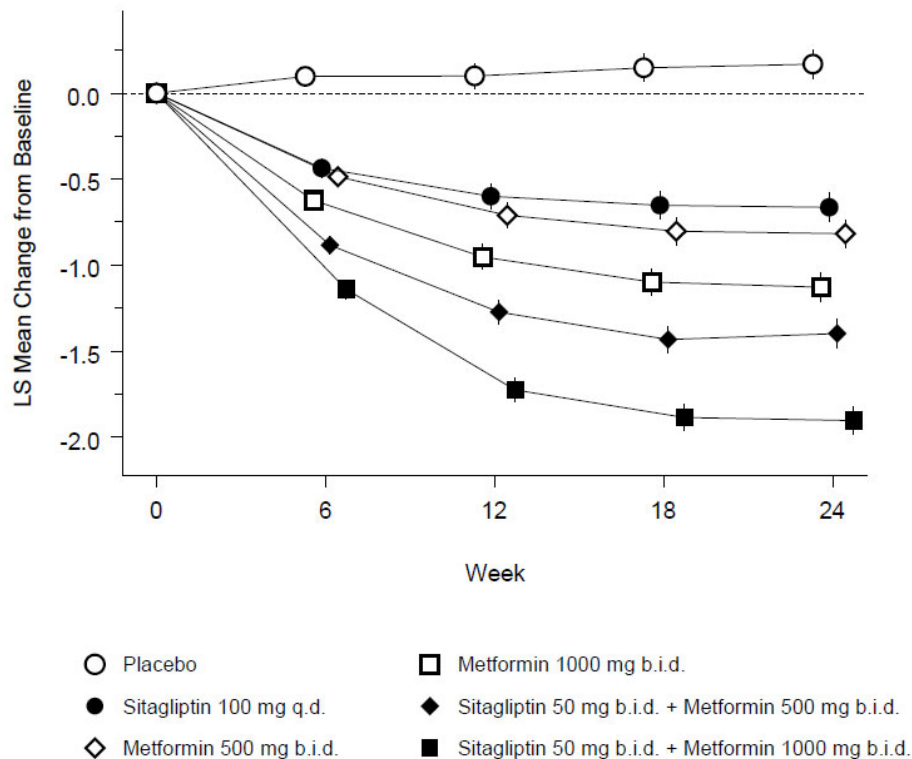
Baseline (mean)	8.7	8.9	8.9	8.7	8.8	8.8
Change from baseline (adjusted mean <sup>†</sup> )	0.2	-0.7	-0.8	-1.1	-1.4	-1.9
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)		-0.8 <sup>§</sup> (-1.1, -0.6)	-1.0 <sup>§</sup> (-1.2, -0.8)	-1.3 <sup>§</sup> (-1.5, -1.1)	-1.6 <sup>§</sup> (-1.8, -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)

<sup>†</sup> 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, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled with Diet and Exercise<sup>†</sup>**



† Intention to Treat 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 Alone

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

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

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

	<b>Sitagliptin 100 mg once daily + Metformin</b>	<b>Placebo + Metformin</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 (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 (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 (adjusted mean <sup>‡</sup> ) (95% CI)	-51 <sup>§</sup> (-61, -41)	

<sup>†</sup> 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 and Glimepiride**

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

Patients receiving sitagliptin with metformin and glimepiride had significant improvements in A1C and FPG compared to patients receiving placebo with metformin and glimepiride (Table 6), with mean reductions from baseline relative to placebo in A1C of -0.9% and in FPG of -21 mg/dL. Rescue therapy was used in 8% of patients treated with add-on sitagliptin 100 mg and 29% of patients treated with add-on placebo. The patients treated with add-on sitagliptin had a mean increase in body weight of 1.1 kg vs. add-on placebo (+0.4 kg vs. -0.7 kg). In addition, add-on sitagliptin resulted in an increased rate of hypoglycemia compared to add-on placebo (see sections 4.4 and 4.8).

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

	<b>Sitagliptin 100 mg + Metformin and Glimepiride</b>	<b>Placebo + Metformin 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)	

<sup>†</sup> 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 and Insulin

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin as add-on to stable-dose insulin therapy. Approximately 75% of patients were also taking metformin. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin ( $\geq 1500$  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, the median daily insulin (pre-mixed, intermediate or long acting) dose at baseline was 40 units in the sitagliptin-treated patients and 42 units in the placebo-treated patients. The median change from baseline in daily dose of insulin was zero for both groups at the end of the study. Patients receiving sitagliptin with metformin and insulin had significant improvements in A1C, FPG and 2-hour PPG compared to patients receiving placebo with metformin and insulin (Table 7). The adjusted mean change from baseline in body weight was -0.3 kg in patients receiving sitagliptin with metformin and insulin and -0.2 kg in patients receiving placebo with metformin and insulin. There was an increased rate of hypoglycemia in patients treated with sitagliptin (see sections 4.4 and 4.8).

**Table 7: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin as Add-on Combination Therapy with Metformin and a Stable Dose of Insulin<sup>†</sup>**

	<b>Sitagliptin 100 mg + Metformin + Insulin</b>	<b>Placebo + Metformin + 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> , <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%	39 (22%)	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)	

<sup>†</sup> 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.

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

Among patients taking metformin, at Week 24, the increase in daily insulin dose was 21% smaller in patients treated with sitagliptin (19 IU/day, N=285) than in patients treated with placebo (24 IU/day, N=283). The reduction in HbA<sub>1c</sub> for patients treated with sitagliptin, metformin, and insulin was -1.35% compared to -0.90% for patients treated with placebo, metformin, and insulin, a difference of -0.45% [95% CI: -0.62, -0.29]. The reduction in FPG for patients treated with sitagliptin, metformin, and insulin was -54.8 mg/dL compared to -43.0 mg/dL for patients treated with placebo, metformin, and insulin, a difference of -11.8 mg/dL [95% CI: -18.7, -4.9]. The incidence of symptomatic hypoglycemia was 24.9% for patients treated with sitagliptin, metformin, and insulin and 37.8% for patients treated with placebo, metformin and insulin. The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycemia (9.1 vs. 19.8%). There was no difference in the incidence of severe hypoglycemia.

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

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

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

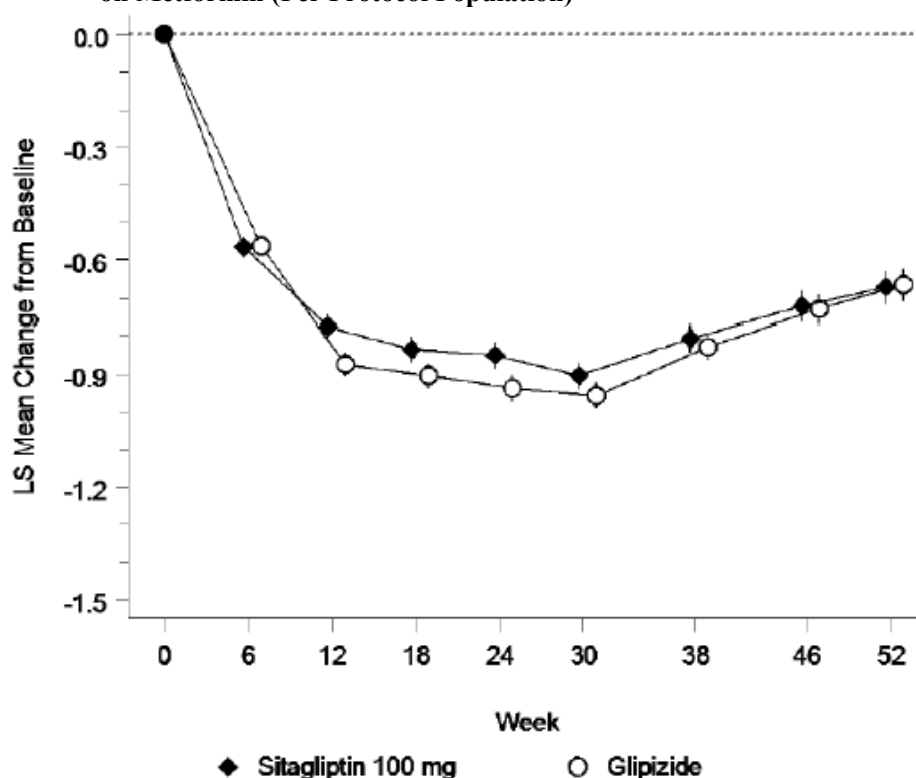
**Table 8: Glycemic Parameters in a 52-Week Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin (Intent-to-Treat Population)<sup>†</sup>**

	<b>Sitagliptin 100 mg + Metformin</b>	<b>Glipizide + Metformin</b>
<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

<sup>†</sup> 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 (Per Protocol Population)<sup>†</sup>**



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

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

**TECOS Cardiovascular Safety Study**

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

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

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

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

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

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

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

\* Incidence rate per 100 patient-years is calculated as  $100 \times (\text{total number of patients with } \geq 1 \text{ event during eligible exposure period per total patient-years of follow-up})$ .

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

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

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

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

Superiority of HbA<sub>1c</sub> reduction was demonstrated for sitagliptin-metformin/ sitagliptin-metformin XR over metformin at Week 20 in the pooled analysis of these two studies. The reduction in HbA<sub>1c</sub> in patients treated with sitagliptin-metformin/ sitagliptin-metformin XR (N=107) was -0.6% compared to -0.1% in patients treated with metformin (N=113), a difference of -0.5% (95% CI: -0.9, -0.1).

However, results from the individual studies were inconsistent, and efficacy for sitagliptin-metformin/ sitagliptin-metformin XR over metformin was not observed at Week 54. These results do not support use of sitagliptin-metformin or sitagliptin-metformin XR in pediatric subjects (10 to 17 years old) with type 2 diabetes.

## **5.2 Pharmacokinetic properties**

### **Absorption**

#### *Sitagliptin*

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

#### *Metformin hydrochloride*



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

### **Distribution**

#### *Sitagliptin*

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

#### *Metformin hydrochloride*

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

### **Metabolism**

#### *Sitagliptin*

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

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

#### *Metformin hydrochloride*

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

### **Excretion**

#### *Sitagliptin*

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

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

mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

#### *Metformin hydrochloride*

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

### ***Special Populations***

#### ***Renal Impairment***

##### *Sitagliptin*

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

#### *Metformin hydrochloride*

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see sections 4.3 and 4.4).

#### ***Hepatic Impairment***

##### *Sitagliptin*

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

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

#### *Metformin hydrochloride*

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

#### ***Gender***

##### *Sitagliptin*

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

#### *Metformin hydrochloride*

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

#### ***Geriatric***

##### *Sitagliptin*

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

### *Metformin hydrochloride*

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

### Pediatric

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

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

### Race

#### *Sitagliptin*

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

### *Metformin hydrochloride*

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

### Body Mass Index (BMI)

#### *Sitagliptin*

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

### ***Drug Interactions***

#### *Sitagliptin and Metformin hydrochloride*

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

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

### *Sitagliptin*

#### *In Vitro Assessment of Drug Interactions*

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

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

## In Vivo Assessment of Drug Interactions

### Effects 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>
No dosing adjustments required for the following:					
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	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 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>
No dosing adjustments required for the following:					
Cyclosporine	600 mg once daily	100 mg once daily	Sitagliptin	1.29	1.68
Metformin	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>

### Effects of Metformin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without metformin) No Effect = 1.00		
				AUC <sup>†</sup>	C <sub>max</sub>
No dosing adjustments required for the following:					
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>

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

¶ Metformin hydrochloride extended-release tablets 500 mg

# Ratio of arithmetic means

### Effects of Coadministered Drugs on Systemic Exposure of Metformin

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC <sup>†</sup>	C <sub>max</sub>
No dosing adjustments required for the following:					
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>
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution (see sections 4.4 and 4.5)					
Cimetidine	400 mg	850 mg	Metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution (see sections 4.4 and 4.5)					
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

‡ Metformin hydrochloride extended-release tablets 500 mg

§ Ratio of arithmetic means

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

### 5.3 Preclinical safety data

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted with sitagliptin/metformin hydrochloride 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, non-dose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison).

#### Metformin hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative. Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Core

Povidone K30  
Sodium lauryl sulfate  
Microcrystalline cellulose  
Croscarmellose sodium  
Sodium stearyl fumarate

#### Coating

Hypromellose, type 2910  
Hydroxypropyl cellulose  
Triethyl citrate  
Titanium dioxide  
Talc  
Ferric oxide red

Additionally, for SITAGLIPTIN-METFORMIN SANDOZ 50 mg/850 mg and SITAGLIPTIN-METFORMIN SANDOZ 50 mg/1000 mg

Ferric oxide yellow

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

Please refer to outer carton.

## **6.4 Special precautions for storage**

Do not store above 30°C.

## **6.5 Nature and contents of container**

Aluminium blisters.

Pack sizes: 28's, 30's, 56's, 60's and 100's.

*Not all pack sizes may be marketed.*

## **6.6 Special precautions for disposal**

No special requirements.

Any unused product or waste should be disposed of in accordance with local requirements.

## **7. MANUFACTURER**

Sandoz Private Limited

MIDC, Plot No. 8-A/2 & 8-B

TTC Industrial Area, Kalwe Block,

400708 Navi Mumbai, India

## **8. DATE OF REVISION OF THE TEXT**

Dec 2022