ZITUVIMET- sitagliptin and metformin hydrochloride tablet, film coated
Zydus Pharmaceuticals (USA) Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZITUVIMET safely and effectively. See full prescribing information for ZITUVIMET.

ZITUVIMET® (sitagliptin and metformin hydrochloride) tablets, for oral use
Initial U.S. Approval: 2007

WARNING: LACTIC ACIDOSIS

***See full prescribing information for complete boxed warning*.**

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL. (5.1)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, hepatic impairment, and mitochondrial diseases. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the Full Prescribing Information. (5.1)**
- **If lactic acidosis is suspected, discontinue ZITUVIMET and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

RECENT MAJOR CHANGES

Boxed Warning	08/2026
Warnings and Precautions, Lactic Acidosis (5.1)	08/2026

INDICATIONS AND USAGE

ZITUVIMET is a combination of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride (HCl), a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)
Limitations of Use:

- ZITUVIMET is not recommended in patients with type 1 diabetes mellitus. (1)
- ZITUVIMET has not been studied in patients with a history of pancreatitis. (1)

DOSAGE AND ADMINISTRATION

- Take ZITUVIMET orally twice daily with meals. (2.1)
- Individualize the dosage of ZITUVIMET on the basis of the patient's current regimen, effectiveness, and tolerability. (2.1)
- The maximum recommended daily dose is 100 mg of sitagliptin and 2,000 mg of metformin HCl. (2.1)
- The recommended starting dose in patients not currently treated with metformin is 50 mg sitagliptin and 500 mg metformin HCl twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin. (2.1)
- The starting dose in patients already treated with metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. For patients taking metformin HCl 850 mg twice daily, the recommended starting dose of ZITUVIMET is 50 mg sitagliptin and 1,000 mg metformin HCl twice daily. (2.1)
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) (2.2)

○ Do not use in patients with eGFR below 30 mL/min/1.73 m^2
○ ZITUVIMET is not recommended in patients with eGFR between 30 and less than 45 mL/min/1.73 m^2.

- ZITUVIMET may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.3)

DOSAGE FORMS AND STRENGTHS

ZITUVIMET Tablets:
- sitagliptin 50 mg and metformin HCl 500 mg tablets
- sitagliptin 50 mg and metformin HCl 1,000 mg tablets (3)

CONTRAINDICATIONS

- Severe renal impairment: (eGFR below 30 mL/min/1.73 m^2) (4)
- Metabolic acidosis, including diabetic ketoacidosis. (4)
- History of a serious hypersensitivity reaction to ZITUVIMET, sitagliptin, or metformin, such as anaphylaxis or angioedema. (4)

WARNINGS AND PRECAUTIONS

- *Lactic Acidosis:* See boxed warning. (5.1)
- *Pancreatitis:* There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue ZITUVIMET. (5.2)
- *Heart Failure*: Has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of ZITUVIMET in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.3)
- *Acute Renal Failure:* Has been reported postmarketing, sometimes requiring dialysis. Before initiating ZITUVIMET and at least annually thereafter, assess renal function. (5.4)
- *Vitamin B_{12} Deficiency:* Metformin may lower vitamin B_{12} levels. Measure hematologic parameters annually and vitamin B_{12} at 2 to 3 year intervals and manage any abnormalities. (5.5)
- *Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues:* Increased risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. A lower dose of insulin or insulin secretagogue may be required. (5.6)
- *Hypersensitivity Reactions:* There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Promptly stop ZITUVIMET, assess for other potential causes, institute appropriate monitoring and treatment. (5.7)
- *Severe and Disabling Arthralgia:* Has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.8)
- *Bullous Pemphigoid:* There have been postmarketing reports requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue ZITUVIMET. (5.9)

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥5% of patients simultaneously started on sitagliptin and metformin and more commonly than in patients treated with placebo were diarrhea, upper respiratory tract infection, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Zydus Pharmaceuticals (USA) Inc. at 1-877-993-8779 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7)

USE IN SPECIFIC POPULATIONS

- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy. (8.3)
- Geriatric Use: Assess renal function more frequently. (8.5)
- Hepatic Impairment: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LACTIC ACIDOSIS
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Recommendations for Use in Renal Impairment
2.3 Discontinuation for Iodinated Contrast Imaging Procedures
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Lactic Acidosis
5.2 Pancreatitis
5.3 Heart Failure
5.4 Acute Renal Failure
5.5 Vitamin B12 Deficiency
5.6 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues
5.7 Hypersensitivity Reactions
5.8 Severe and Disabling Arthralgia
5.9 Bullous Pemphigoid
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

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

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, hepatic impairment, and mitochondrial diseases *[see Warnings and Precautions (5.1)]*.

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

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

1 INDICATIONS AND USAGE

ZITUVIMET is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

ZITUVIMET is not recommended in patients with type 1 diabetes mellitus.

ZITUVIMET 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 ZITUVIMET. *[see Warnings and Precautions (5.2)].*

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- Take ZITUVIMET orally twice daily with meals.
- Individualize the dosage of ZITUVIMET on the basis of the patient's current regimen,

effectiveness, and tolerability.
- The maximum recommended daily dose is 100 mg of sitagliptin and 2,000 mg of metformin hydrochloride (HCl).
- Do not split or divide ZITUVIMET tablets.
- The recommended starting dose in patients not currently treated with metformin is 50 mg sitagliptin and 500 mg metformin HCl twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin.
- The starting dose in patients already treated with metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. For patients taking metformin HCl 850 mg twice daily, the recommended starting dose of ZITUVIMET is 50 mg sitagliptin and 1,000 mg metformin HCl twice daily.

2.2 Recommendations for Use in Renal Impairment

- Assess renal function prior to initiation of ZITUVIMET and periodically thereafter.
- ZITUVIMET is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 *[see Contraindications (4) and Warnings and Precautions (5.1)].*
- ZITUVIMET is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m^2 because these patients require a lower dosage of sitagliptin than what is available in the fixed combination ZITUVIMET product.

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue ZITUVIMET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; 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 ZITUVIMET if renal function is stable *[see Warnings and Precautions (5.1)].*

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- sitagliptin 50 mg and metformin HCl 500 mg tablets are white to off-white, oval shaped, biconvex, film coated tablets debossed with "1786" on one side and plain on the other side.
- sitagliptin 50 mg and metformin HCl 1,000 mg tablets are reddish brown, oval shaped, biconvex, film coated tablets debossed with "1787" on one side and plain on the other side.

4 CONTRAINDICATIONS

ZITUVIMET is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) *[see Warnings and Precautions (5.1)].*
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis.
- History of a serious hypersensitivity reaction to sitagliptin, metformin, or any of the excipients in ZITUVIMET. Serious hypersensitivity reactions including anaphylaxis or

angioedema have been reported. *[see Warnings and Precautions (5.7) and Adverse Reactions (6.2)].*

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

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

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

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

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

Renal Impairment

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

- Before initiating ZITUVIMET, obtain an estimated glomerular filtration rate (eGFR).
- ZITUVIMET is contraindicated in patients with an eGFR below 30 mL/min/1.73 m^2 *[see Contraindications (4)].*
- ZITUVIMET is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m^2 because these patients require a lower dosage of sitagliptin than what is available in the fixed combination ZITUVIMET product.
- Obtain an eGFR at least annually in all patients taking ZITUVIMET. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions

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

Age 65 or Greater

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

Radiological Studies with Contrast

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

Surgery and Other Procedures

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

Hypoxic States

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

Excessive Alcohol Intake

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

Hepatic Impairment

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

Mitochondrial Diseases: Metformin may increase the risk of lactic acidosis in patients with mitochondrial diseases such as mitochondrial encephalomyopathy with lactic acidosis, and stroke-like episodes (MELAS) syndrome and maternally inherited diabetes and deafness (MIDD). ZITUVIMET is not recommended in patients with mitochondrial

diseases such as MELAS syndrome and MIDD.

If a patient taking ZITUVIMET develops elevated lactic acid levels (with or without accompanying neurologic signs and symptoms), discontinue ZITUVIMET. Depending on the clinical context, consider evaluating the patient for MELAS, MIDD, or other mitochondrial disease.

5.2 Pancreatitis

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

5.3 Heart Failure

An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of ZITUVIMET prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of ZITUVIMET.

5.4 Acute Renal Failure

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with ZITUVIMET and at least annually thereafter, renal function should be assessed. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and ZITUVIMET discontinued if evidence of renal impairment is present. ZITUVIMET is contraindicated in patients with severe renal impairment *[see Contraindications (4) and Warnings and Precautions (5.1)].*

5.5 Vitamin B12 Deficiency

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

5.6 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues

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

5.7 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of ZITUVIMET. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose.

If a hypersensitivity reaction is suspected, discontinue ZITUVIMET, assess for other potential causes for the event, and institute alternative treatment for diabetes. *[see Adverse Reactions (6.2)].*

Angioedema has also been reported with other DPP-4 inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with ZITUVIMET.

5.8 Severe and Disabling Arthralgia

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

5.9 Bullous Pemphigoid

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

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere in the prescribing information:

- Lactic Acidosis *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Heart Failure *[see Warnings and Precautions (5.3)]*
- Acute Renal Failure *[see Warnings and Precautions (5.4)]*
- Vitamin B12 Deficiency *[see Warnings and Precautions (5.5)]*
- Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues *[see Warnings and Precautions (5.6)]*

- Hypersensitivity Reactions *[see Warnings and Precautions (5.7)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (5.8)]*
- Bullous Pemphigoid *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

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

Common Adverse Reactions

Sitagliptin and Metformin Coadministration in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise

Table 1 summarizes the most common (≥5% of patients) adverse reactions reported in a 24-week placebo-controlled factorial trial in which sitagliptin and metformin were coadministered to patients with type 2 diabetes mellitus inadequately controlled on diet and exercise.

Table 1: Sitagliptin and Metformin Coadministered to Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise: Adverse Reactions Reported in ≥5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)*

	Number of Patients (%)			
	Placebo	**Sitagliptin 100 mg once daily**	**Metformin HCl 500 mg/ Metformin HCl 1,000 mg twice daily†**	**Sitagliptin 50 mg twice daily + Metformin HCl 500 mg/ Metformin HCl 1,000 mg twice daily†**
	N = 176	**N = 179**	**N = 364†**	**N = 372†**
Diarrhea	7 (4)	5 (2.8)	28 (7.7)	28 (7.5)
Upper Respiratory Tract Infection	9 (5.1)	8 (4.5)	19 (5.2)	23 (6.2)
Headache	5 (2.8)	2 (1.1)	14 (3.8)	22 (5.9)

* Intent-to-treat population.
† Data pooled for the patients given the lower and higher doses of metformin.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Mellitus 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 in ≥5% of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse reactions was similar to the placebo treatment group (sitagliptin and metformin, 1.9%; placebo and metformin, 2.5%).

Gastrointestinal Adverse Reactions

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

Table 2: Pre-selected Gastrointestinal Adverse Reactions Reported in Patients with Type 2 Diabetes Mellitus Receiving Sitagliptin and Metformin

	Number of Patients (%)					
	Trial of Sitagliptin and Metformin in Patients Inadequately Controlled on Diet and Exercise				Trial of Sitagliptin Add-on in Patients Inadequately Controlled on Metformin Alone	
	Placebo	Sitagliptin 100 mg once daily	Metformin HCl 500 mg/ Metformin HCl 1,000 mg twice daily*	Sitagliptin 50 mg twice daily + Metformin HCl 500 mg/ Metformin HCl 1,000 mg twice daily*	Placebo and Metformin HCl ≥1,500 mg daily	Sitagliptin 100 mg once daily and Metformin HCl ≥1,500 mg daily
	N = 176	N = 179	N = 364	N = 372	N = 237	N = 464
Diarrhea	7 (4)	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)	2 (0.5)	8 (2.2)	2 (0.8)	5 (1.1)
Abdominal Pain†	4 (2.3)	6 (3.4)	14 (3.8)	11 (3)	9 (3.8)	10 (2.2)

* Data pooled for the patients given the lower and higher doses of metformin.
† Abdominal discomfort was included in the analysis of abdominal pain in the trial of initial therapy.

Sitagliptin in Combination with Metformin and Glimepiride

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

Sitagliptin in Combination with Metformin and Rosiglitazone

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

placebo were: upper respiratory tract infection (sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%).

Sitagliptin in Combination with Metformin and Insulin

In a 24-week placebo-controlled trial of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin and insulin (sitagliptin, N=229; placebo, N=233), the only adverse reaction reported in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycemia (Table 3).

Hypoglycemia

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

Table 3: Incidence and Rate of Hypoglycemia* in Placebo-Controlled Clinical Trials of Sitagliptin in Combination with Metformin Coadministered with Glimepiride or Insulin

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

* Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required: Intent-to-treat population.
† Based on total number of events (i.e., a single patient may have had multiple events).
‡ Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

The overall incidence of reported adverse reactions of hypoglycemia in patients with type 2 diabetes mellitus 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 mellitus 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.

In the trial of sitagliptin and add-on combination therapy with metformin and rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on sitagliptin and 0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on sitagliptin and 1% in patients given add-on placebo.

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

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=5,429) or corresponding (active or placebo) control (N=4,817), the incidence of acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4,708 patient-years for sitagliptin and 4 patients with an event in 3,942 patient-years for control).

Sitagliptin

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

Metformin

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

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 trials, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6,600 cells/microL) was observed due to a small increase in neutrophils. This change in laboratory parameters is not considered to be clinically relevant.

Metformin

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

6.2 Postmarketing Experience

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

Skin and subcutaneous tissue disorders: hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome; bullous pemphigoid;

Respiratory, thoracic and mediastinal disorders: upper respiratory tract infection;

Hepatobiliary disorders: hepatic enzyme elevations; cholestatic, hepatocellular, and mixed hepatocellular liver injury;

Gastrointestinal disorders: acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis *[see Indications and Usage (1)];* constipation; vomiting; mouth ulceration; stomatitis;

Renal and urinary disorders: worsening renal function, including acute renal failure (sometimes requiring dialysis) and tubulointerstitial nephritis;

Musculoskeletal and connective tissue disorders: severe and disabling arthralgia; myalgia; pain in extremity; back pain; pruritus; rhabdomyolysis;

Nervous system disorders: headache.

7 DRUG INTERACTIONS

Table 4 presents clinically significant drug interactions with ZITUVIMET:

Table 4: Clinically Significant Drug Interactions with ZITUVIMET	
Carbonic Anhydrase Inhibitors	
Clinical Impact:	Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with ZITUVIMET may increase the risk for lactic acidosis.
Intervention:	Consider more frequent monitoring of these patients.
Examples:	Topiramate, zonisamide, acetazolamide or dichlorphenamide.
Drugs that Reduce Metformin Clearance	
Clinical Impact:	Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT_2] / multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)].*
Intervention:	Consider the benefits and risks of concomitant use with ZITUVIMET.
Examples:	Ranolazine, vandetanib, dolutegravir, and cimetidine.
Alcohol	
Clinical Impact:	Alcohol is known to potentiate the effect of metformin on lactate

	metabolism.
Intervention:	Warn patients against alcohol intake while receiving ZITUVIMET.
Insulin Secretagogues or Insulin	
Clinical Impact:	Coadministration of ZITUVIMET with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia.
Intervention:	Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.
Drugs Affecting Glycemic Control	
Clinical Impact:	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.
Intervention:	When such drugs are administered to a patient receiving ZITUVIMET, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving ZITUVIMET, observe the patient closely for hypoglycemia.
Examples:	Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with ZITUVIMET and sitagliptin use in pregnant women are not sufficient to inform a ZITUVIMET-associated or sitagliptin-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk *[see Data].* There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations].* No adverse developmental effects were observed when sitagliptin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 30-times and 20-times, respectively, the 100 mg clinical dose, based on AUC. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during organogenesis at doses up to 2- and 6-times, respectively, a 2,000 mg clinical dose, based on body surface area *[see Data].*

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a hemoglobin A1c (A1C) >7% and has been reported to be as high as 20% to 25% in women with a A1C >10%. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20% respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects,

still birth, and macrosomia related morbidity.

Data

Human Data

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

Animal Data

Sitagliptin and Metformin

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

Sitagliptin

In embryo-fetal development studies, sitagliptin administered to pregnant rats and rabbits during organogenesis (gestation day 6 to 20) did not adversely affect developmental outcomes at oral doses up to 250 mg/kg (30-times the 100 mg clinical dose) and 125 mg/kg (20-times the 100 mg clinical dose), respectively, based on AUC. Higher doses in rats associated with maternal toxicity increased the incidence of rib malformations in offspring at 1,000 mg/kg, or approximately 100-times the clinical dose, based on AUC. Placental transfer of sitagliptin was observed in pregnant rats and rabbits.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 caused no functional or behavioral toxicity in offspring of rats at doses up to 1,000 mg/kg.

Metformin

Metformin did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2- and 6-times a 2,000 mg clinical dose based on body surface area (mg/m^2) for rats and rabbits, respectively.

8.2 Lactation

Risk Summary

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

Data

Sitagliptin

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

Metformin

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

8.3 Females and Males of Reproductive Potential

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

8.4 Pediatric Use

The safety and effectiveness of ZITUVIMET have not been established in pediatric patients.

Pediatric information describing clinical studies in which efficacy was not demonstrated is approved for Merck Sharp and Dohme's JANUMET (sitagliptin and metformin hydrochloride) tablets. However, due to Merck Sharp and Dohme's marketing exclusivity rights, this drug product is not labeled with that information.

8.5 Geriatric Use

ZITUVIMET

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

Sitagliptin

Of the total number of subjects (N=3,884) in clinical studies of sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness of sitagliptin have been observed between subjects 65 years and over and younger patients.

Metformin

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

8.6 Renal Impairment

ZITUVIMET

ZITUVIMET is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m^2 because these patients require a lower dosage of sitagliptin than what is

available in the fixed dose combination ZITUVIMET product. ZITUVIMET is contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.2) >, Contraindications (4)>, Warnings and Precautions (5.1)> and Clinical Pharmacology (12.3)].*

Sitagliptin

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

Metformin

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

In the event of overdose with ZITUVIMET, consider contacting the Poison Help Line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. Employ the usual supportive measures dictated by the patient's clinical status. Per clinical judgement, consider removal of unabsorbed material from the gastrointestinal tract, and clinical monitoring (including obtaining an ECG).

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

Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases *[see Warnings and Precautions (5.1)].* Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

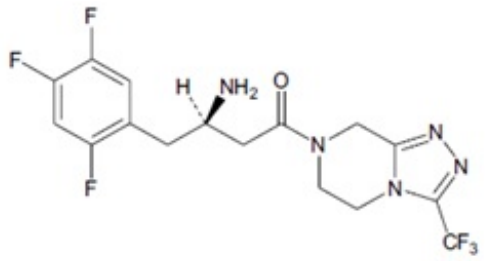
11 DESCRIPTION

ZITUVIMET (sitagliptin and metformin HCl) tablets for oral use contain sitagliptin and metformin HCl.

Sitagliptin

Sitagliptin is an orally-active inhibitor of DPP-4 enzyme. Sitagliptin is present in ZITUVIMET tablets in the form of sitagliptin free base. Sitagliptin free base is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3 (trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine with an empirical formula of $C_{16}H_{15}F_6N_5O$

and a molecular weight of 407.31. The structural formula is:

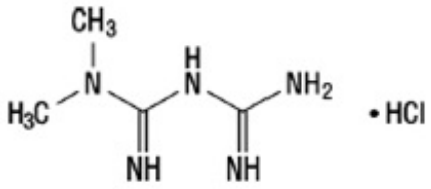


Sitagliptin free base is a white to off-white, non-hygroscopic powder. It is soluble in methanol and slightly soluble in water.

Metformin HCl USP

Metformin HCl, USP (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin HCl, USP is a white crystalline powder with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.62. Metformin HCl is freely soluble in water, slightly soluble in ethanol (95%), practically insoluble in acetone and in methylene chloride. The pKa of metformin HCl is 12.4. The pH of a 1% aqueous solution of metformin HCl is 6.68.

The structural formula is as shown:



ZITUVIMET is available as film-coated tablets containing:

- 50 mg of sitagliptin and 389.93 mg of metformin equivalent to 500 mg metformin HCl (ZITUVIMET 50/500).
- 50 mg of sitagliptin and 779.86 mg of metformin equivalent to 1,000 mg metformin HCl (ZITUVIMET 50/1,000).

Each film-coated tablet of ZITUVIMET contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, low substituted hydroxypropylcellulose, magnesium stearate, malic acid, microcrystalline cellulose, povidone, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The film coating of 50 mg/1,000 mg also contains: FD&C yellow #6 aluminum lake, iron oxide red, and iron oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZITUVIMET

ZITUVIMET combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: sitagliptin, a DPP- 4 inhibitor, and metformin HCl, a member of the biguanide class.

Sitagliptin

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

Metformin

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

12.2 Pharmacodynamics

Sitagliptin

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

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

Sitagliptin and Metformin Coadministration

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

Cardiac Electrophysiology

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

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

12.3 Pharmacokinetics

Sitagliptin

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

Absorption

Sitagliptin

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

Effect of Food

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

Metformin

The absolute bioavailability of a metformin HCl 500-mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin HCl tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg (approximately 1.3 times the maximum recommended daily dosage), indicate that there is a lack of dose

proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Effect of Food

Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850-mg tablet of metformin HCl with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Sitagliptin

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

Metformin

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin HCl tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin HCl tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL.

Elimination

Sitagliptin

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. The apparent terminal $t_{1/2}$ following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Metformin

Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metabolism

Sitagliptin

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

Metformin

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

Excretion

Sitagliptin

Following administration of an oral [^{14}C] sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing.

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

Metformin

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

Specific Populations

Patients with Renal Impairment

ZITUVIMET

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

Sitagliptin

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to less than 45 mL/min/1.73 m^2, and an approximately 4-fold increase was observed in patients with severe renal impairment including patients with end-stage renal disease (ESRD) on hemodialysis, as compared to normal healthy control subjects. *[see Dosage and Administration (2.2)].*

Metformin

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

Patients with Hepatic Impairment

ZITUVIMET

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

Sitagliptin

In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of sitagliptin. These differences are not considered to be clinically meaningful. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score >9) *[see Use in Specific Populations (8.7)].*

Metformin

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

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

Sitagliptin

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

Metformin

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

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

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

Drug Interaction Studies

ZITUVIMET

Coadministration of multiple doses of sitagliptin (50 mg) and metformin HCl (1,000 mg) given twice daily did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes mellitus.

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

Sitagliptin

In Vitro Assessment of Drug Interactions

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

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

In Vivo Assessment of Drug Interactions

Effects of Sitagliptin on Other Drugs

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

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

Coadministered Drug	**Dose of Coadministered Drug***	**Dose of Sitagliptin***	**Geometric Mean Ratio (ratio with/without sitagliptin) No Effect = 1**		
				AUC†	**C_{max}**
Digoxin	0.25 mg‡ once daily for 10 days	100 mg‡ once daily for 10 days	Digoxin	1.11§	1.18
Glyburide	1.25 mg	200 mg‡ once daily for 6 days	Glyburide	1.09	1.01
Simvastatin	20 mg	200 mg‡ once daily for 5 days	Simvastatin	0.85¶	0.8
			Simvastatin Acid	1.12¶	1.06
Rosiglitazone	4 mg	200 mg‡ once daily for 5 days	Rosiglitazone	0.98	0.99
Warfarin	30 mg single dose on day 5	200 mg‡ 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 mg x 7 days	200 mg‡ once daily for 21 days	Ethinyl estradiol	0.99	0.97
			Norethindrone	1.03	0.98
Metformin HCl	1,000 mg‡ twice daily for 14 days	50 mg‡ twice daily for 7 days	Metformin	1.02#	0.97

* All doses administered as single dose unless otherwise specified.
† AUC is reported as $AUC_{0-\infty}$ unless otherwise specified.
‡ Multiple dose.
§ AUC_{0-24hr}.
¶ AUC_{0-last}.

AUC_{0-12hr}.

Effects of Other Drugs on Sitagliptin

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

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

Coadministered Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1		
				AUC†	C_{max}
Cyclosporine	600 mg once daily	100 mg once daily	Sitagliptin	1.29	1.68
Metformin HCl	1,000 mg‡ twice daily for 14 days	50 mg‡ twice daily for 7 days	Sitagliptin	1.02§	1.05

* All doses administered as single dose unless otherwise specified.
† AUC is reported as $AUC_{0-\infty}$ unless otherwise specified.
‡ Multiple dose.
§ AUC_{0-12hr}.

Metformin HCl

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

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without metformin) No Effect = 1		
				AUC†	C_{max}
Cimetidine	400 mg	850 mg	Cimetidine	0.95‡	1.01
Glyburide	5 mg	500 mg§	Glyburide	0.78¶	0.63¶
Furosemide	40 mg	850 mg	Furosemide	0.87¶	0.69¶
Nifedipine	10 mg	850 mg	Nifedipine	1.10‡	1.08
Propranolol	40 mg	850 mg	Propranolol	1.01‡	0.94
Ibuprofen	400 mg	850 mg	Ibuprofen	0.97#	1.01#

* All doses administered as single dose unless otherwise specified.
† AUC is reported as $AUC_{0-\infty}$ unless otherwise specified.
‡ AUC_{0-24hr}.
§ GLUMETZA (metformin HCl extended-release tablets) 500 mg.
¶ Ratio of arithmetic means, p value of difference <0.05.
# Ratio of arithmetic means.

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

			Geometric Mean Ratio

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	(ratio with/without coadministered drug) No Effect = 1		
				AUC†	C_{max}
Glyburide	5 mg	500 mg‡	Metformin‡	0.98§	0.99§
Furosemide	40 mg	850 mg	Metformin	1.09§	1.22§
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§	1.07§
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin. *[see Warnings and Precautions (5.1) and Drug Interactions (7)].*					
Cimetidine	400 mg	850 mg	Metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis *[see Warnings and Precautions (5.1) and Drug Interactions (7)].*					
Topiramate	100 mg¶	500 mg¶	Metformin	1.25¶	1.17

* All doses administered as single dose unless otherwise specified.
† AUC is reported as $AUC_{0-\infty}$ unless otherwise specified.
‡ GLUMETZA (metformin HCl extended-release tablets) 500 mg.
§ Ratio of arithmetic means.
¶ Steady state 100 mg Topiramate every 12 hr + metformin HCl 500 mg every 12 hr AUC = AUC_{0-12hr}.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ZITUVIMET

No animal studies have been conducted with the combined products in ZITUVIMET 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 1,000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination

(approximately 8 weeks total), and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, nondose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison).

Metformin

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2,000 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.

14 CLINICAL STUDIES

The coadministration of sitagliptin and metformin has been evaluated in patients with type 2 diabetes mellitus inadequately controlled on diet and exercise and in combination with other antihyperglycemic agents.

Sitagliptin and Metformin Coadministration in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise

A total of 1,091 patients with type 2 diabetes mellitus and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind, placebo-controlled factorial trial designed to assess the efficacy of sitagliptin and metformin coadministration. Patients on an antihyperglycemic agent (N=541) underwent a diet, exercise, and drug washout period of up to 12 weeks duration. After the washout period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized after completing a 2-week single-blind placebo run-in period. Patients not on anti-hyperglycemic agents at trial 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 1,000 mg of metformin HCl twice daily, or 50 mg of sitagliptin twice daily in combination with 500 mg or 1,000 mg of metformin HCl twice daily. Patients who failed to meet specific glycemic goals during the trial were treated with glyburide (glibenclamide) rescue.

Sitagliptin and metformin coadministration provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to sitagliptin alone

(Table 9, 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 trial entry, mean reductions from baseline in A1C were: sitagliptin 100 mg once daily, -1.1%; metformin HCl 500 mg bid, -1.1%; metformin HCl 1,000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin HCl 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin HCl 1,000 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.

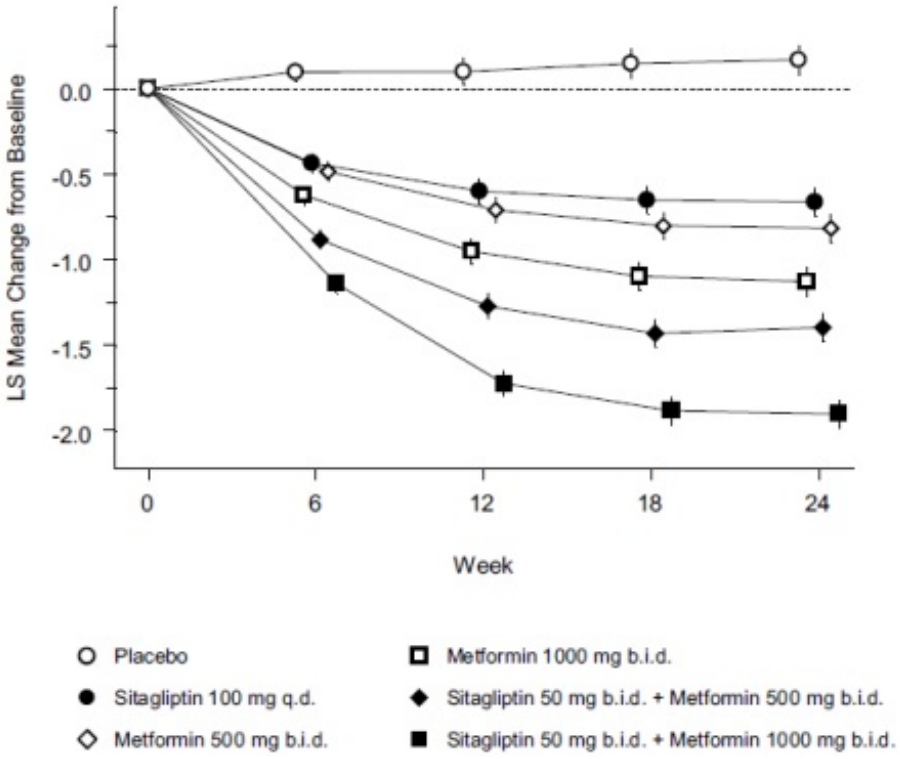
Table 9: Glycemic Parameters at Final Visit (24-Week Trial) for Sitagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise*

	Placebo	**Sitagliptin 100 mg once daily**	**Metformin HCl 500 mg twice daily**	**Metformin HCl 1,000 mg twice daily**	**Sitagliptin 50 mg twice daily + Metformin HCl 500 mg twice daily**	**Sitagliptin 50 mg twice daily + Metformin HCl 1,000 mg twice daily**
A1C (%)	**N = 165**	**N = 175**	**N = 178**	**N = 177**	**N = 183**	**N = 178**
Baseline (mean)	8.7	8.9	8.9	8.7	8.8	8.8
Change from baseline (adjusted mean†)	0.2	-0.7	-0.8	-1.1	-1.4	-1.9
Difference from placebo (adjusted mean†) (95% CI)		-0.8‡ (-1.1, -0.6)	-1‡ (-1.2, -0.8)	-1.3‡ (-1.5, -1.1)	-1.6‡ (-1.8, -1.3)	-2.1‡ (-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
FPG (mg/dL)	**N = 169**	**N = 178**	**N = 179**	**N = 179**	**N = 183**	**N = 180**
Baseline (mean)	196	201	205	197	204	197
Change from baseline (adjusted mean†)	6	-17	-27	-29	-47	-64
Difference from placebo (adjusted mean†) (95% CI)		-23‡ (-33, -14)	-33‡ (-43, -24)	-35‡ (-45, -26)	-53‡ (-62, -43)	-70‡ (-79, -60)

2-hour PPG (mg/dL)	N = 129	N = 136	N = 141	N = 138	N = 147	N = 152
Baseline (mean)	277	285	293	283	292	287
Change from baseline (adjusted mean†)	0	-52	-53	-78	-93	-117
Difference from placebo (adjusted mean†) (95% CI)		-52‡ (-67, -37)	-54‡ (-69, -39)	-78‡ (-93, -63)	-93‡ (-107, -78)	-117‡ (-131, -102)

* Intent-to-treat population using last observation in the trial prior to glyburide (glibenclamide) rescue therapy.
† Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
‡ 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 Mellitus Inadequately Controlled with Diet and Exercise*



*All Patients Treated 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 Mellitus Inadequately Controlled on Metformin Alone

A total of 701 patients with type 2 diabetes mellitus participated in a 24-week, randomized, double-blind, placebo-controlled trial designed to assess the efficacy of sitagliptin in combination with metformin. Patients already on metformin (N=431) at a dose of at least 1,500 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 HCl (at a dose of at least 1,500 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 10). Rescue glycemic therapy was used in 5% of patients treated with sitagliptin 100 mg and 14% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table 10: Glycemic Parameters at Final Visit (24-Week Trial) of Sitagliptin as Add-on Combination Therapy with Metformin*

	Sitagliptin 100 mg once daily + Metformin	**Placebo + Metformin**
A1C (%)	**N = 453**	**N = 224**
Baseline (mean)	8	8
Change from baseline (adjusted mean†)	-0.7	-0
Difference from placebo + metformin (adjusted mean†) (95% CI)	-0.7‡ (-0.8, -0.5)	
Patients (%) achieving A1C <7%	213 (47%)	41 (18%)
FPG (mg/dL)	**N = 454**	**N = 226**
Baseline (mean)	170	174
Change from baseline (adjusted mean†)	-17	9
Difference from placebo + metformin (adjusted mean†) (95% CI)	-25‡ (-31, -20)	
2-hour PPG (mg/dL)	**N = 387**	**N = 182**
Baseline (mean)	275	272
Change from baseline (adjusted mean†)	-62	-11
Difference from placebo + metformin (adjusted mean†) (95% CI)	-51‡ (-61, -41)	

* Intent-to-treat population using last observation on trial prior to pioglitazone rescue therapy.
† Least squares means adjusted for prior antihyperglycemic therapy and baseline value.
‡ p<0.001 compared to placebo + metformin.

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

A total of 441 patients with type 2 diabetes mellitus participated in a 24-week, randomized, double-blind, placebo-controlled trial 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 HCl (≥1,500 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 11), with mean reductions from baseline relative to placebo in A1C of -0.9% and in FPG of -21 mg/dL. Rescue therapy was used in 8% of patients treated with add-on sitagliptin 100 mg and 29% of patients treated with add-on placebo. The patients treated with add-on sitagliptin had a mean increase in body weight of 1.1 kg vs. add-on placebo (+0.4 kg vs. -0.7 kg). In addition, add-on sitagliptin resulted in an increased rate of hypoglycemia compared to add-on placebo. *[see Warnings and Precautions (5.6) and Adverse Reactions (6.1)].*

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

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

* Intent-to-treat population using last observation on trial prior to pioglitazone rescue therapy.
† Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
‡ p<0.001 compared to placebo.

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

A total of 278 patients with type 2 diabetes mellitus participated in a 54-week, randomized, double-blind, placebo-controlled trial designed to assess the efficacy of sitagliptin in combination with metformin and rosiglitazone. Patients on dual therapy with metformin HCl ≥1,500 mg/day and rosiglitazone ≥4 mg/day or with metformin HCl ≥1,500 mg/day and pioglitazone ≥30 mg/day (switched to rosiglitazone ≥4 mg/day) entered a dose-stable run-in period of 6 weeks. Patients on other dual therapy were

switched to metformin HCl ≥1,500 mg/day and rosiglitazone ≥4 mg/day in a dose titration/stabilization run-in period of up to 20 weeks in duration. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized 2:1 to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the trials were treated with glipizide (or other sulfonylurea) rescue. The primary time point for evaluation of glycemic parameters was Week 18.

In combination with metformin and rosiglitazone, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin and rosiglitazone (Table 12) at Week 18. At Week 54, mean reduction in A1C was -1% for patients treated with sitagliptin and -0.3% for patients treated with placebo in an analysis based on the intent-to-treat population. Rescue therapy was used in 18% of patients treated with sitagliptin 100 mg and 40% of patients treated with placebo. There was no significant difference between sitagliptin and placebo in body weight change.

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

	Week 18	
	Sitagliptin 100 mg + Metformin + Rosiglitazone	**Placebo + Metformin + Rosiglitazone**
A1C (%)	**N = 176**	**N = 93**
Baseline (mean)	8.8	8.7
Change from baseline (adjusted mean†)	-1	-0.4
Difference from placebo + rosiglitazone + metformin (adjusted mean†) (95% CI)	-0.7‡ (-0.9,-0.4)	
Patients (%) achieving A1C <7%	39 (22%)	9 (10%)
FPG (mg/dL)	**N = 179**	**N = 94**
Baseline (mean)	181	182
Change from baseline (adjusted mean†)	-30	-11
Difference from placebo + rosiglitazone + metformin (adjusted mean†) (95% CI)	-18‡ (-26, -10)	
2-hour PPG (mg/dL)	**N = 152**	**N = 80**
Baseline (mean)	256	248
Change from baseline (adjusted mean†)	-59	-21
Difference from placebo + rosiglitazone + metformin (adjusted mean†) (95% CI)	-39‡ (-51, -26)	

* Intent-to-treat population using last observation in the trial prior to glipizide (or other sulfonylurea) rescue therapy.
† Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
‡ p<0.001 compared to placebo + metformin + rosiglitazone.

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

A total of 641 patients with type 2 diabetes mellitus participated in a 24-week, randomized, double-blind, placebo-controlled trial designed to assess the efficacy of

sitagliptin as add-on to 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 HCl (≥1,500 mg per day). Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a pre-mixed insulin. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized to the addition of either 100 mg of sitagliptin (N=229) or placebo (N=233), administered once daily. Patients were on a stable dose of insulin prior to enrollment with no changes in insulin dose permitted during the run-in period. Patients who failed to meet specific glycemic goals during the double-blind treatment period were to have uptitration of the background insulin dose as rescue therapy.

Among patients also receiving metformin, the median daily insulin (pre-mixed, intermediate or long acting) dose at baseline was 40 units in the sitagliptin-treated patients and 42 units in the placebo-treated patients. The median change from baseline in daily dose of insulin was zero for both groups at the end of the trial. 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 13). The adjusted mean change from baseline in body weight was -0.3 kg in patients receiving sitagliptin with metformin and insulin and -0.2 kg in patients receiving placebo with metformin and insulin. There was an increased rate of hypoglycemia in patients treated with sitagliptin. *[see Warnings and Precautions (5.6) and Adverse Reactions (6.1)].*

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

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

* Intent-to-treat population using last observation on trial prior to rescue therapy.
† 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.
‡ Treatment by insulin stratum interaction was not significant (p >0.10).

§ p<0.001 compared to placebo.

Maintenance of Sitagliptin During Initiation and Titration of Insulin Glargine

A total of 746 patients with type 2 diabetes (mean baseline HbA1C 8.8%, disease duration 10.8 years) participated in a 30-week, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of continuing sitagliptin during the initiation and uptitration of insulin glargine. Patients who were on a stable dose of metformin HCl (≥1,500 mg/day) in combination with a DPP-4 inhibitor and/or sulfonylurea but with inadequate glycemic control (A1C 7.5% to 11%) were enrolled in the study. Those on metformin and sitagliptin (100 mg/day) directly entered the double-blind treatment period; those on another DPP-4 inhibitor and/or on a sulfonylurea entered a 4 to 8 week run-in period in which they were maintained on metformin and switched to sitagliptin (100 mg); other DPP-4 inhibitors and sulfonylureas were discontinued. At randomization patients were randomized either to continue sitagliptin or to discontinue sitagliptin and switch to a matching placebo. On the day of randomization, insulin glargine was initiated at a dose of 10 units subcutaneously in the evening. Patients were instructed to uptitrate their insulin dose in the evening based on fasting blood glucose measurements to achieve a target of 72 to 100 mg/dL.

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

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

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

* N is the number of randomized and treated patients.
† Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputation to model washout of the treatment effect using placebo data for all subjects having missing Week 30 data.
‡ p<0.001 compared to placebo.

Sitagliptin Add-on Therapy vs. Glipizide Add-on Therapy in Patients with Type

2 Diabetes Mellitus 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 mellitus. 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 ≥1,500 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.

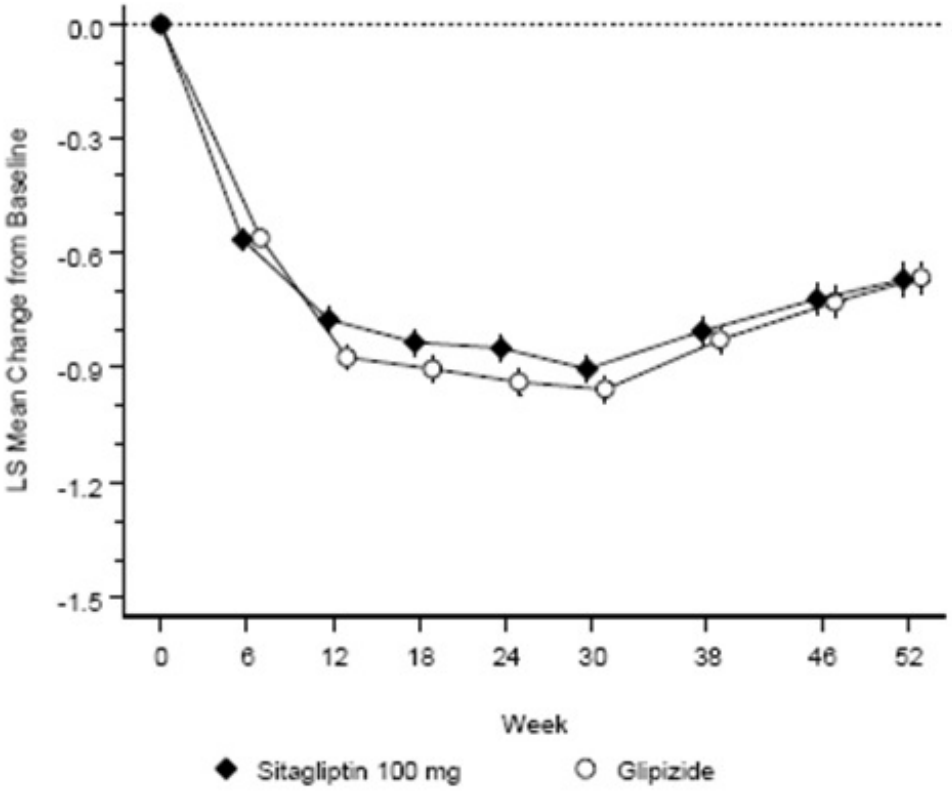
After 52 weeks, sitagliptin and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis (Table 15). These results were consistent with the per protocol analysis (Figure 2). A conclusion in favor of the non-inferiority of sitagliptin to glipizide may be limited to patients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

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

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

* The intent-to-treat analysis used the patients' last observation in the trial prior to discontinuation.
† 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 Trial Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin (Per Protocol Population)*



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

The incidence of hypoglycemia in the sitagliptin group (4.9%) was significantly ($p<0.001$) lower than that in the glipizide group (32%). Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs. +1.1 kg).

16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets supplied as follows:

Contents	Description	How Supplied	NDC
50 mg sitagliptin and 500 mg metformin HCl	White to off-white, oval shaped, biconvex, film coated tablets debossed with "1786" on one side and plain on the other side.	Bottles of 60 tablets with child-resistant closure.	NDC 70710-1786-6
		Bottles of 180 tablets with child-resistant closure.	NDC 70710-1786-8
50 mg sitagliptin and 1,000 mg metformin HCl	Reddish brown, oval shaped, biconvex, film coated tablets debossed with	Bottles of 60 tablets with child-resistant closure.	NDC 70710-1787-6
		Bottles of 180 tablets with child-	NDC 70710-1787-8

	"1787" on one side and plain on the other side	resistant closure.	

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F), [see USP Controlled Room Temperature].

Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Lactic Acidosis

Explain the risks of lactic acidosis, its symptoms, and conditions that predispose to its development. Advise patients to discontinue ZITUVIMET immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Counsel patients against excessive alcohol intake and inform patients about the importance of regular testing of renal function while receiving ZITUVIMET. Instruct patients to inform their doctor that they are taking ZITUVIMET prior to any surgical or radiological procedure, as temporary discontinuation may be required *[see Warnings and Precautions (5.1)].*

Pancreatitis

Inform patients that acute pancreatitis has been reported during postmarketing use of sitagliptin. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to promptly discontinue ZITUVIMET and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.2)].*

Heart Failure

Inform patients of the signs and symptoms of heart failure. Before initiating ZITUVIMET, ask patients about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Instruct patients to contact their health care provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet *[see Warnings and Precautions (5.3)].*

Vitamin B_{12} Deficiency

Inform patients about the importance of regular monitoring of hematological parameters while receiving ZITUVIMET *[see Warnings and Precautions (5.5)].*

Hypoglycemia

Inform patients that the incidence of hypoglycemia is increased when ZITUVIMET is added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. Explain to patients receiving ZITUVIMET in combination with these medications the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development *[see Warnings and Precautions (5.6)].*

Hypersensitivity Reactions

Inform patients that allergic reactions have been reported during postmarketing use of sitagliptin, one of the components of ZITUVIMET. If symptoms of allergic reactions (including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking ZITUVIMET and seek medical advice promptly.

Severe and Disabling Arthralgia

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs *[see Warnings and Precautions (5.8)].*

Bullous Pemphigoid

Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur *[see Warnings and Precautions (5.9)].*

Females of Reproductive Age:

Inform females that treatment with ZITUVIMET may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy *[see Use in Specific Populations (8.3)].*

Administration Instructions

Inform patients that the tablets must never be split or divided before swallowing.

The trademarks depicted herein are owned by their respective companies.

Medication Guide available at www.zydususa.com/medguides/ or call 1-877-993-8779

Manufactured by:

Zydus Lifesciences Ltd.,

Pharmez, Matoda, Ahmedabad, India.

Distributed by:

Zydus Pharmaceuticals (USA) Inc.

Route 31 North, Pennington, NJ 08534

Medication Guide **ZITUVIMET® (zye too' vi met)** **(sitagliptin and metformin hydrochloride)** **tablets, for oral use**
Read this Medication Guide carefully before you start taking ZITUVIMET and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have any questions about ZITUVIMET, ask your healthcare provider or pharmacist
What is the most important information I should know about ZITUVIMET? **ZITUVIMET can cause serious side effects , including:**

1. Lactic Acidosis. Metformin, one of the medicines in ZITUVIMET, can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Stop taking ZITUVIMET and call your healthcare provider right away if you have any of the following symptoms, which could be signs of lactic acidosis:

- you feel cold in your hands or feet
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you feel sleepy or drowsy
- you have stomach pains, nausea or vomiting

Most people who have had lactic acidosis with metformin have other things that, combined with the metformin, led to the lactic acidosis. Tell your healthcare provider if you have any of the following, because you have a higher chance for getting lactic acidosis with ZITUVIMET if you:

- have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye have liver problems
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea.
- Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have surgery
- have a heart attack, severe infection, or stroke
- are 65 years of age or older
- have a genetically inherited disease affecting mitochondria (the energy-producing parts within cells) such as mitochondrial encephalomyopathy with lactic acidosis, and stroke-like episodes (MELAS) syndrome and maternally inherited diabetes and deafness (MIDD).

The best way to keep from having a problem with lactic acidosis from metformin is to tell your healthcare provider if you have any of the problems in the list above. Your healthcare provider may decide to stop your ZITUVIMET for a while if you have any of these things. ZITUVIMET can have other serious side effects. See **"What are the possible side effects of ZITUVIMET?"**

2. Inflammation of the pancreas (pancreatitis) which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.

Before you start taking ZITUVIMET, tell your healthcare provider if you have ever had:

- pancreatitis
- stones in your gallbladder (gallstones)
- high blood triglyceride levels
- a history of alcoholism
- kidney problems

Stop taking ZITUVIMET and call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

3. Heart failure. Heart failure means that your heart does not pump blood well enough.

Before you start taking ZITUVIMET, tell your healthcare provider if you have ever had heart failure or have problems with your kidneys. Contact your healthcare provider right away if you have any of the following symptoms:

- increasing shortness of breath or trouble breathing, especially when you lie down
- swelling or fluid retention, especially in the feet, ankles, or legs
- an unusually fast increase in weight
- unusual tiredness

These may be symptoms of heart failure.

What is ZITUVIMET?

- ZITUVIMET is a prescription medicine that contains 2 prescription diabetes medicines, sitagliptin and metformin that is used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- ZITUVIMET is not for people with type 1 diabetes.
- If you have had pancreatitis (inflammation of the pancreas) in the past, it is not known if you have a higher chance of getting pancreatitis while you take ZITUVIMET
- It is not known if ZITUVIMET is safe and effective in children .

Who should not take ZITUVIMET?

Do not take ZITUVIMET if you:

- have severe kidney problems.
- have diabetic ketoacidosis.
- are allergic to any of the ingredients in ZITUVIMET. See the end of this Medication Guide for a complete list of ingredients in ZITUVIMET.

Symptoms of a serious allergic reaction to ZITUVIMET may include rash, raised red patches on your skin (hives) or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.

What should I tell my healthcare provider before taking ZITUVIMET?

Before you take ZITUVIMET, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had inflammation of your pancreas (pancreatitis).
- have kidney problems.
- have liver problems.
- have heart failure.
- drink alcohol very often or drink a lot of alcohol in short-term "binge" drinking.
- are going to get an injection of dye or contrast agents for an x-ray procedure. ZITUVIMET may need to be stopped for a short time. Talk to your healthcare provider about when you should stop ZITUVIMET and when you should start ZITUVIMET again. See " **What is the most important information I should know about ZITUVIMET?** "
- have low levels of vitamin B12 in your blood.
- are pregnant or plan to become pregnant. It is not known if ZITUVIMET will harm

your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if ZITUVIMET will pass into your breast milk. Talk with your healthcare provider about the best way to feed your baby if you are taking ZITUVIMET.
- are a woman who has not gone through menopause (premenopausal) who does not have periods regularly or at all. ZITUVIMET can cause the release of an egg from an ovary in a woman (ovulation). This can increase your chance of getting pregnant. Tell your healthcare provider right away if you become pregnant while taking ZITUVIMET.
- have a genetically inherited disease affecting mitochondria (the energy-producing parts within cells) such as MELAS syndrome and MIDD.

Tell your healthcare provider about all the medicines you take , including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZITUVIMET may affect the way other medicines work and other medicines may affect how ZITUVIMET works.
Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take ZITUVIMET?
- Take ZITUVIMET 2 times a day by mouth. Your healthcare provider will tell you exactly how many ZITUVIMET tablets to take and when you should take them.
- Take ZITUVIMET with meals to help to lower your chance of having an upset stomach.
- Do not break or cut ZITUVIMET tablets before swallowing. If you cannot swallow ZITUVIMET tablets whole, tell your healthcare provider.
- Your healthcare provider may tell you to take ZITUVIMET along with certain other diabetes medicines. Low blood sugar (hypoglycemia) can happen more often when ZITUVIMET is taken with certain other diabetes medicines. See "What are the possible side effects of ZITUVIMET?".
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection or surgery, the amount of diabetes medicine that you need may change. Tell your healthcare provider right away if you have any of these problems and follow your healthcare provider's instructions.
- Your healthcare provider will do blood tests to check how well your kidneys are working before and during your treatment with ZITUVIMET
- If you take too much ZITUVIMET, call your healthcare provider or Poison Help Line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of ZITUVIMET?
ZITUVIMET may cause serious side effects, including:
- see **"What is the most important information I should know about ZITUVIMET?".**
- **kidney problems,** sometimes requiring dialysis.
- **low vitamin B_{12} (vitamin B_{12} deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B_{12} in your blood, especially if you have had low vitamin B_{12} blood levels before. Your healthcare provider may do blood tests to check your vitamin B_{12} levels.
- **low blood sugar (hypoglycemia).** If you take ZITUVIMET with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting

low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you use ZITUVIMET. Signs and symptoms of low blood sugar may include:

- o headache
- o hunger
- o sweating
- o fast heart beat
- o drowsiness
- o dizziness
- o feeling jittery
- o irritability
- o confusion
- o weakness

- **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking ZITUVIMET and call your healthcare provider right away or get emergency medical help. See " **Who should not take** ZITUVIMET?". Your healthcare provider may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.
- **Joint pain.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in ZITUVIMET, may develop joint pain that can be severe. Call your healthcare provider if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in ZITUVIMET, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your healthcare provider right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your healthcare provider may tell you to stop taking ZITUVIMET.

The most common side effects of ZITUVIMET include:

- stuffy or runny nose and sore throat
- upper respiratory infection
- low blood sugar (hypoglycemia) when used in combination with certain medicines, such as a sulfonylurea or insulin
- gas, upset stomach, indigestion
- weakness
- nausea and vomiting
- headache
- diarrhea

Taking ZITUVIMET with meals can help lessen the common stomach side effects of metformin that usually happen at the beginning of treatment. If you have unusual or sudden stomach problems, talk with your healthcare provider. Stomach problems that start later during treatment may be a sign of something more serious.

ZITUVIMET may have other side effects, including swelling of the hands or legs . Swelling of the hands and legs can happen if you take ZITUVIMET in combination with rosiglitazone (Avandia). Rosiglitazone is another type of diabetes medicine.

Tell your healthcare provider if you have any side effect that bothers you, or does not go away.

These are not all the possible side effects of ZITUVIMET. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZITUVIMET?

- Store ZITUVIMET at room temperature, between 68°F to 77°F (20°C to 25°C).
- Protect it from moisture.

Keep ZITUVIMET and all medicines out of the reach of children.

General information about the safe and effective use of ZITUVIMET.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ZITUVIMET for a condition for which it was not prescribed. Do not give ZITUVIMET to other people, even if they have the same symptoms you have. It may harm them.
. You can ask your healthcare provider or pharmacist for information about ZITUVIMET that is written for health professionals.

What are the ingredients in ZITUVIMET?
Active ingredients: sitagliptin and metformin hydrochloride
Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, low substituted hydroxypropylcellulose, magnesium stearate, malic acid, microcrystalline cellulose, povidone, and sodium stearyl fumarate.
In addition, the film coating contains the following inactive ingredients: polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The film coating of 50 mg/1,000 mg also contains: FD&C yellow #6 aluminum lake, iron oxide red, and iron oxide yellow.

Manufactured by: Zydus Lifesciences Ltd., Pharmez, Matoda, Ahmedabad, India
Distributed by: Zydus Pharmaceuticals (USA) Inc., Route 31 North, Pennington, NJ 08534
The trademarks depicted herein are owned by their respective companies.
For more information, call 1-877-993-8779, email medicalaffairs@zydusua.com, or go to www.zyususa.com/medguides/

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Revised: 08/2026

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 70710-1786-6 in bottle of 60 tablets with child-resistant closure.

Zituvimet®

(sitagliptin and metformin HCl) tablets, 50 mg/500 mg

Dispense the enclosed Medication Guide to each patient.

Rx only

Zydus

NDC 70710-1787-6 in bottle of 60 tablets with child-resistant closure.

Zituvimet®

(sitagliptin and metformin HCl) tablets, 50 mg/1000 mg

Dispense the enclosed Medication Guide to each patient.

Rx only

Zydus

ZITUVIMET

sitagliptin and metformin hydrochloride tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70710-1786
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
SITAGLIPTIN (UNII: QFP0P1DV7Z) (SITAGLIPTIN - UNII:QFP0P1DV7Z)	SITAGLIPTIN	50 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	500 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 120000 MW) (UNII: NZ94SDL6WR)	

MAGNESIUM STEARATE (UNII: 70097M6I30)	
MALIC ACID (UNII: 817L1N4CKP)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL 3350 (UNII: G2M7P15E5P)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
POVIDONE K30 (UNII: U725QWY32X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	WHITE (white to off-white)	**Score**	no score
Shape	OVAL	**Size**	17mm
Flavor		**Imprint Code**	1786
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70710-1786-6	60 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2024	
2	NDC:70710-1786-8	180 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2024	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA216743	03/14/2024	

ZITUVIMET

sitagliptin and metformin hydrochloride tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70710-1787
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SITAGLIPTIN (UNII: QFP0P1DV7Z) (SITAGLIPTIN - UNII:QFP0P1DV7Z)	SITAGLIPTIN	50 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	1000 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE (11% HYDROXYPROPYL; 120000 MW) (UNII: NZ94SDL6WR)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MALIC ACID (UNII: 817L1N4CKP)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL 3350 (UNII: G2M7P15E5P)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
POVIDONE K30 (UNII: U725QWY32X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	BROWN (reddish brown)	**Score**	no score
Shape	OVAL	**Size**	21mm
Flavor		**Imprint Code**	1787
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70710-1787-6	60 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2024	
2	NDC:70710-1787-8	180 in 1 BOTTLE; Type 0: Not a Combination Product	03/14/2024	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA216743	03/14/2024	

Labeler - Zydus Pharmaceuticals (USA) Inc. (156861945)

Registrant - Zydus Lifesciences Global FZE (850107010)

Establishment

Name	Address	ID/FEI	Business Operations

Zydus Lifesciences Limited		863362789	ANALYSIS(70710-1786, 70710-1787) , MANUFACTURE(70710-1786, 70710-1787)

Revised: 7/2026 Zydus Pharmaceuticals (USA) Inc.