ZITUVIO- sitagliptin tablet
Zydus Lifesciences Limited

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

ZITUVIO (sitagliptin) tablets, for oral use
Initial U.S. Approval: 2006

INDICATIONS AND USAGE

ZITUVIO is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)
Limitations of Use:

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

DOSAGE AND ADMINISTRATION

The recommended dosage of ZITUVIO is 100 mg orally once daily. ZITUVIO can be taken with or without food. (2.1)
Dosage adjustment is recommended for patients with eGFR less than 45 mL/min/1.73 m^2. (2.2)

Dosage Adjustment in Patients with Renal Impairment (2.2)	
eGFR greater than or equal to 30 mL/min/1.73 m^2 to less than 45 mL/min/1.73 m^2	eGFR less than 30 mL/min/1.73 m^2 (including patients with end stage renal disease [ESRD] on dialysis)
50 mg once daily	25 mg once daily

DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg, 50 mg, and 25 mg (3)

CONTRAINDICATIONS

History of a serious hypersensitivity reaction to sitagliptin or any of the excipients in ZITUVIO, such as anaphylaxis or angioedema (4)

WARNINGS AND PRECAUTIONS

- *Pancreatitis:* There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue ZITUVIO. (5.1)
- *Heart failure:* Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of ZITUVIO in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.2)
- *Acute Renal Failure:*Has been reported postmarketing, sometimes requiring dialysis. Assessment of renal function is recommended prior to initiating ZITUVIO and periodically thereafter. (5.3)
- *Hypoglycemia with Concomitant Use with Insulin or InsulinSecretagogues:* Increased risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. Lower dose of insulin or insulin secretagogue may be required. (5.4)
- *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 ZITUVIO, assess for other potential causes, institute appropriate monitoring and treatment. (5.5)
- *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. (5.6)
- *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 ZITUVIO. (5.7)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5%) are: upper respiratory tract infection, nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with sitagliptin compared to placebo. (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.
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Limitations of Use

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

ZITUVIO 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 ZITUVIO. *[see Warnings and Precautions (5.1)].*

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of ZITUVIO is 100 mg orally once daily. ZITUVIO can be taken with or without food.

2.2 Recommendations for Use in Renal Impairment

Assess renal function prior to initiation of ZITUVIO and periodically thereafter.

For patients with an estimated glomerular filtration rate [eGFR] greater than or equal to 45 mL/min/1.73 $m^2$to less than 90 mL/min/1.73 m^2, no dosage adjustment for ZITUVIO is required.

For patients with moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 $m^2$to less than 45 mL/min/1.73 m^2), the dosage of ZITUVIO is 50 mg once daily.

For patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dosage of ZITUVIO is 25 mg once daily. ZITUVIO may be administered without regard to the timing of dialysis.

3 DOSAGE FORMS AND STRENGTHS

- 100 mg tablets are beige, round, biconvex, film coated tablets debossed with "12" on one side and "42" on the other side.
- 50 mg tablets are pale yellow, round, biconvex, film coated tablets debossed with "12" on one side and "41" on the other side.
- 25 mg tablets are white to off white, round, biconvex, film coated tablets debossed with "12" on one side and "40" on the other side.

4 CONTRAINDICATIONS

ZITUVIO is contraindicated in patients with a history of a serious hypersensitivity reaction to sitagliptin or any of the excipients in ZITUVIO. Serious hypersensitivity reactions, including anaphylaxis and angioedema have been reported with sitagliptin. *[see Warnings and Precautions (5.5); Adverse Reactions (6.2)].*

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

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

5.2 Heart Failure

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

Consider the risks and benefits of ZITUVIO 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 ZITUVIO.

5.3 Acute Renal Failure

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal impairment, some of whom were prescribed inappropriate doses of sitagliptin.

A return to baseline levels of renal impairment has been observed with supportive treatment and discontinuation of potentially causative agents. Consideration can be given to cautiously reinitiating ZITUVIO if another etiology is deemed likely to have precipitated the acute worsening of renal function.

Assessment of renal function is recommended prior to initiating ZITUVIO and periodically thereafter. A dosage adjustment is recommended in patients with moderate or severe renal impairment and in patients with ESRD requiring hemodialysis or peritoneal dialysis. *[see Dosage and Administration (2.2); Use in Specific Populations (8.6)].*

5.4 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues

When sitagliptin was used in combination with insulin or insulin secretagogues (e.g., sulfonylurea), medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. *[see Adverse Reactions (6.1)].* Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycaemia when used in combination with ZITUVIO. *[see Drug Interactions (7.1)].*

5.5 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin. 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 ZITUVIO, 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 ZITUVIO.

5.6 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.

5.7 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 ZITUVIO. If bullous pemphigoid is suspected, ZITUVIO 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:

- Pancreatitis *[see Warnings and Precautions (5.1)]*
- Heart Failure *[see Warnings and Precautions (5.2)]*
- Acute Renal Failure *[see Warnings and Precautions (5.3)]*
- Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (5.6)]*
- Bullous Pemphigoid *[see Warnings and Precautions (5.7)]*

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

In controlled clinical trials as both monotherapy and combination therapy with metformin, pioglitazone, or rosiglitazone and metformin, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to clinical adverse reactions with sitagliptin were similar to placebo. In combination with glimepiride, with or without metformin, the overall incidence of clinical adverse reactions with sitagliptin was higher than with placebo, in part related to a higher incidence of hypoglycemia (see Table 3); the incidence of discontinuation due to clinical adverse reactions was similar to placebo.

Two placebo-controlled monotherapy trials, one of 18- and one of 24-week duration, included patients treated with sitagliptin 100 mg daily, sitagliptin 200 mg daily, and placebo. Five placebo-controlled add-on combination therapy trials were also conducted: one with metformin; one with pioglitazone; one with metformin and rosiglitazone; one with glimepiride (with or without metformin); and one with insulin (with or without metformin). In these trials, patients with inadequate glycemic control on a stable dosage of the background therapy were randomized to add-on therapy with sitagliptin 100 mg daily or placebo. The adverse reactions, excluding hypoglycemia, reported in ≥5% of patients treated with sitagliptin 100 mg daily and more commonly than in patients treated with placebo, are shown in Table 1 for the clinical trials of at least 18 weeks duration. Incidences of hypoglycemia are shown in Table 3.

Table 1: Placebo-Controlled Clinical Trials of Sitagliptin Monotherapy or Add-on Combination Therapy with Pioglitazone, Metformin + Rosiglitazone, or Glimepiride +/-Metformin: Adverse Reactions (Excluding Hypoglycemia) Reported in ≥5% of Patients and More Commonly than in Patients Given Placebo*

	Number of Patients (%)	
Monotherapy (18 or 24 weeks)	**Sitagliptin 100 mg**	**Placebo**
	N = 443	N = 363
Nasopharyngitis	23 (5.2)	12 (3.3)
Combination with Pioglitazone (24 weeks)	**Sitagliptin 100 mg + Pioglitazone**	**Placebo + Pioglitazone**
	N = 175	N = 178
Upper Respiratory Tract Infection	11 (6.3)	6 (3.4)
Headache	9 (5.1)	7 (3.9)
Combination with Metformin + Rosiglitazone (18 weeks)	**Sitagliptin 100 mg + Metformin + Rosiglitazone**	**Placebo + Metformin + Rosiglitazone**
	N = 181	N = 97
Upper Respiratory Tract Infection	10 (5.5)	5 (5.2)
Nasopharyngitis	11 (6.1)	4 (4.1)
Combination with Glimepiride (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Glimepiride (+/- Metformin)**	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Nasopharyngitis	14 (6.3)	10 (4.6)
Headache	13 (5.9)	5 (2.3)

* Intent-to-treat population

In the 24-week trial of patients receiving sitagliptin as add-on combination therapy with metformin, there were no adverse reactions reported in ≥5% of patients and more

commonly than in patients given placebo.

In the 24-week trial of patients receiving sitagliptin as add-on therapy to insulin (with or without metformin), there were no adverse reactions reported in ≥5% of patients and more commonly than in patients given placebo, except for hypoglycemia (see Table 3).

In the trial of sitagliptin as add-on combination therapy with metformin and rosiglitazone (Table 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%).

In an additional, 24-week, placebo-controlled factorial trial of initial therapy with sitagliptin in combination with metformin, the adverse reactions reported in ≥5% of patients are shown in Table 2.

Table 2: Initial Therapy with Combination of Sitagliptin and Metformin: Adverse Reactions Reported in ≥5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Metformin alone, Sitagliptin alone, and Placebo)*

	Number of Patients (%)			
	Placebo	**Sitagliptin 100 mg QD**	**Metformin HCl 500 or 1,000 mg bid†**	**Sitagliptin 50 mg bid + Metformin HCl 500 or 1,000 mg bid†**
	N = 176	N = 179	N = 364†	N = 372†
Upper Respiratory 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.

In a 24-week trial of initial therapy with sitagliptin in combination with pioglitazone, there were no adverse reactions reported in ≥5% of patients and more commonly than in patients given pioglitazone alone.

Other Adverse Reactions

Hypoglycemia

In the above trials (N=9), adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia. A concurrent blood glucose measurement was not required although most (74%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL. When sitagliptin was coadministered with a sulfonylurea or with insulin, the percentage of patients with at least one adverse reaction of hypoglycemia was higher than in the corresponding placebo group (Table 3).

Table 3: Incidence and Rate of Hypoglycemia*in Placebo-Controlled Clinical Trials when Sitagliptin was used as Add-On Therapy to Glimepiride (with or without Metformin) or Insulin (with or without Metformin)

Add-On to Glimepiride (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Glimepiride (+/- Metformin)**	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Overall (%)	27 (12.2)	4 (1.8)
Rate (episodes/patient-year)†	0.59	0.24
Severe (%)‡	0 (0)	0 (0)
Add-On to Insulin (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Insulin (+/- Metformin)**	**Placebo + Insulin (+/- Metformin)**
	N = 322	N = 319

Overall (%)	50 (15.5)	25 (7.8)
Rate (episodes/patient-year)†	1.06	0.51
Severe (%)‡	2 (0.6)	1 (0.3)

* 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.

In a pooled analysis of the two monotherapy trials, the add-on to metformin trial, and the add-on to pioglitazone trial, the overall incidence of adverse reactions of hypoglycemia was 1.2% in patients treated with sitagliptin 100 mg and 0.9% in patients treated with placebo.

In the trial of sitagliptin as 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 sitagliptin and 1% in patients given add-on placebo.

In the 24-week, placebo-controlled factorial trial of initial therapy with sitagliptin in combination with metformin, the incidence of hypoglycemia 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 the trial of sitagliptin as initial therapy with pioglitazone, one patient taking ZITUVIO experienced a severe episode of hypoglycemia. There were no severe hypoglycemia episodes reported in other trials except in the trial involving coadministration with insulin.

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.

Gastrointestinal Adverse Reactions

In a pooled analysis of the two monotherapy trials, the add-on to metformin trial, and the add-on to pioglitazone trial, the incidence of selected gastrointestinal adverse reactions in patients treated with sitagliptin was as follows: abdominal pain (ZITUVIO 100 mg, 2.3%; placebo, 2.1%),

nausea (1.4%, 0.6%), and diarrhea (3%, 2.3%).

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).

Vital Sign and Electrocardiogram (EGC) Changes

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with sitagliptin

<u>Laboratory Tests</u>

Across clinical trials, the incidence of laboratory adverse reactions was similar in patients treated with sitagliptin 100 mg compared to patients treated with placebo. A small increase in white blood cell count (WBC) was observed due to an increase in neutrophils. This increase in WBC (of approximately 200 cells/microL vs placebo, in four pooled placebo-controlled clinical trials, with a mean baseline WBC count of approximately 6,600 cells/microL) is not considered to be clinically relevant. In a 12-week trial of 91 patients with chronic renal insufficiency, 37 patients with moderate renal insufficiency were randomized to sitagliptin 50 mg daily, while 14 patients with the same magnitude of renal impairment were randomized to placebo. Mean (SE) increases in serum creatinine were

observed in patients treated with sitagliptin [0.12 mg/dL (0.04)] and in patients treated with placebo [0.07 mg/dL (0.07)]. The clinical significance of this added increase in serum creatinine relative to placebo is not known.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of sitagliptin as monotherapy and/or in combination with other antihyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

Hepatobiliary disorders: hepatic enzyme elevations

Gastrointestinal disorders: acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis, constipation; vomiting, mouth ulceration, and 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

7.1 Insulin Secretagogues or Insulin

Sitagliptin lowers blood glucose in patients with type 2 diabetes mellitus. Coadministration of ZITUVIO with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia. *[see Warnings and Precautions (5.4)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with sitagliptin in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. 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 *[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, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Animal Data

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.

8.2 Lactation

Risk Summary

There is no information regarding the presence of sitagliptin in human milk, the effects on the breastfed infant, or the effects 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 ZITUVIO and any potential adverse effects on the breastfed infant from ZITUVIO or from the underlying maternal condition.

Data

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

8.4 Pediatric Use

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

Pediatric information describing clinical trials in which efficacy was not demonstrated is approved for Merck Sharp and Dohme's JANUVIA (sitagliptin) 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

Of the total number of subjects (N=3,884) in pre-approval clinical safety and efficacy trials 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

patients 65 years and over and younger patients.

Because sitagliptin is substantially excreted by the kidney, and because aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*

8.6 Renal Impairment

Sitagliptin is excreted by the kidney, and sitagliptin exposure is increased in patients with renal impairment. Lower dosages are recommended in patients with eGFR less than 45 mL/min/1.73 m^2(moderate and severe renal impairment, as well as in ESRD patients requiring dialysis). *[see Dosage and Administration (2.2); Clinical Pharmacology (12.3)].*

10 OVERDOSAGE

In the event of an overdose with ZITUVIO, 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 judgment, consider removal of unabsorbed material from the gastrointestinal tract and clinical monitoring (including obtaining an ECG).

Sitagliptin is modestly dialyzable. In clinical trials, approximately 13.5% of the dose was

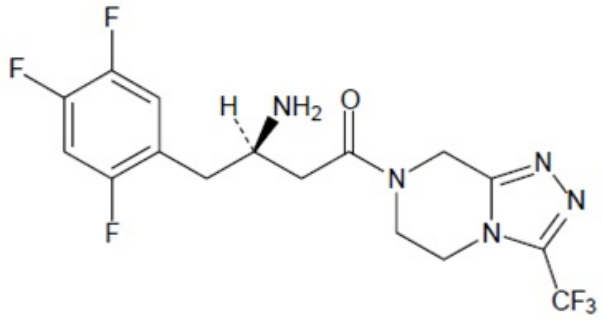
removed over a 3-to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

11 DESCRIPTION

ZITUVIO Tablets contain sitagliptin free base, an orally active inhibitor of the DPP-4 enzyme.

Sitagliptin free base is described chemically as 7-[(3*R*)-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.

The empirical formula is $C_{16}H_{15}F_6N_5O$ and the molecular weight is 407.31. The structural formula is:



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

Each film coated tablet of ZITUVIO contains sitagliptin free base 25 mg, 50 mg, or 100 mg as active ingredient and the following inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, croscarmellose sodium, malic acid, magnesium stearate, microcrystalline cellulose, and povidone. In addition, the film coating contains the following inactive ingredients: polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The 50 mg tablet's film coating also contains ferrosoferric oxide and iron oxide yellow. The 100 mg tablet's film coating also contains FD&C Yellow #6 Aluminum Lake and iron oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.2 Pharmacodynamics

General

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 hydrochloride 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 how these findings relate to 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 was observed at 3 hours postdose and was 8 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

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.

<u>Absorption</u>

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.

<u>Distribution</u>

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%).

<u>Elimination</u>

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.

Metabolism

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.

Excretion

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.

Specific Populations

Patients with Renal Impairment

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 ESRD on hemodialysis, as compared to normal healthy control subjects.

Patients with Hepatic Impairment

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).

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

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.

Drug Interaction Studies

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 contraceptive (ethinyl estradiol and norethindrone) (Table 4), 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 4: 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¶	0.80
			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 5).

Table 5: 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 drugs) 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}.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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, non-dose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison).

14 CLINICAL STUDIES

There were approximately 5,200 patients with type 2 diabetes mellitus randomized in nine double-blind, placebo-controlled clinical safety and efficacy trials conducted to evaluate the effects of sitagliptin on glycemic control. In a pooled analysis of seven of these trials, the ethnic/racial distribution was approximately 59% White, 20% Hispanic or Latino ethnicity, 10% Asian, 6% Black or African American, and 6% other groups. Patients had an overall mean age of approximately 55 years (range 18 to 87 years). In addition, an active (glipizide)-controlled trial of 52-weeks duration was conducted in 1,172 patients with type 2 diabetes mellitus who had inadequate glycemic control on metformin.

In patients with type 2 diabetes mellitus, treatment with sitagliptin produced clinically significant improvements inA1C, fasting plasma glucose (FPG) and 2-hour post-prandial glucose (PPG) compared to placebo.

14.1 Monotherapy

A total of 1,262 patients with type 2 diabetes mellitus participated in two double-blind, placebo-controlled trials, one of 18-week and another of 24-week duration, to evaluate the efficacy and safety of sitagliptin monotherapy. In both monotherapy trials, patients currently on an antihyperglycemic agent discontinued the agent, and underwent a diet, exercise, and drug washout period of about 7 weeks. Patients with inadequate glycemic control (A1C 7% to 10%) after the washout period were randomized after completing a 2-week single-blind placebo run-in period; patients not currently on antihyperglycemic agents (off therapy for at least 8 weeks) with inadequate glycemic control (A1C 7% to 10%) were randomized after completing the 2-week single-blind placebo run-in period. In the 18-week trial, 521 patients were randomized to placebo, sitagliptin 100 mg, or sitagliptin 200 mg, and in the 24-week trial 741 patients were randomized to placebo, sitagliptin 100 mg, or sitagliptin 200 mg. Patients who failed to meet specific glycemic

goals during the trials were treated with metformin rescue, added on to placebo or sitagliptin.

Treatment with sitagliptin at 100 mg daily provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo (Table 6). In the 18-week trial, 9% of patients receiving sitagliptin 100 mg and 17% who received placebo required rescue therapy. In the 24-week trial, 9% of patients receiving sitagliptin 100 mg and 21% of patients receiving placebo required rescue therapy. The improvement in A1C compared to placebo was not affected by gender, age, race, prior antihyperglycemic therapy, or baseline BMI. In these 18-and 24-week trials, among patients who were not on an antihyperglycemic agent at trial entry, the reductions from baseline in A1C were -0.7% and -0.8%, respectively, for those given sitagliptin, and -0.1% and -0.2%, respectively, for those given placebo. Overall, the 200 mg daily dose did not provide greater glycemic efficacy than the 100 mg daily dose. The effect of sitagliptin on lipid endpoints was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy in either trial, compared to a small reduction in patients given placebo.

Table 6: Glycemic Parameters in 18- and 24-Week Placebo-Controlled Trials of Sitagliptin in Patients with Type 2 Diabetes Mellitus*

	18-Week Trial		**24-Week Trial**	
	Sitagliptin 100 mg	**Placebo**	**Sitagliptin 100 mg**	**Placebo**
A1C (%)	**N = 193**	**N = 103**	**N = 229**	**N = 244**
Baseline (mean)	8	8.1	8	8
Change from baseline (adjusted mean†)	-0.5	0.1	-0.6	0.2
Difference from placebo (adjusted mean†) (95% CI)	-0.6‡ (-0.8, -0.4)		-0.8‡ (-1.0, -0.6)	
Patients (%) achieving A1C <7%	69 (36%)	16 (16%)	93 (41%)	41 (17%)
FPG (mg/dL)	**N = 201**	**N = 107**	**N = 234**	**N = 247**
Baseline (mean)	180	184	170	176
Change from baseline (adjusted mean†)	-13	7	-12	5
Difference from placebo (adjusted mean†) (95% CI)	-20‡ (-31, -9)		-17‡ (-24, -10)	
2-hour PPG (mg/dL)	§	§	**N = 201**	**N = 204**
Baseline (mean)			257	271
Change from baseline (adjusted mean†)			-49	-2
Difference from placebo (adjusted mean†) (95% CI)			-47‡ (-59, -34)	

* Intent-to-treat population using last observation on trial prior to metformin rescue therapy.
† Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
‡ p<0.001 compared to placebo.
§ Data not available.

Additional Monotherapy Trial

A multinational, randomized, double-blind, placebo-controlled trial was also conducted to assess the safety and tolerability of sitagliptin in 91 patients with type 2 diabetes mellitus and chronic renal insufficiency (creatinine clearance <50 mL/min). Patients with moderate renal insufficiency received 50 mg daily of sitagliptin and those with severe renal insufficiency or with ESRD on hemodialysis or peritoneal dialysis received 25 mg daily. In this trial, the safety and tolerability of sitagliptin were generally similar to placebo. A small increase in serum creatinine was reported in patients with moderate renal insufficiency treated with sitagliptin relative to those on placebo. In addition, the reductions in A1C and FPG with sitagliptin compared to placebo were generally similar to those observed in other monotherapy trials. *[see Clinical Pharmacology (12.3)].*

14.2 Combination Therapy

Add-on Combination Therapy with Metformin

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 HCl (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 anti-hyperglycemic 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 with inadequate glycemic control (A1C 7% to 10%) 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 trials 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 7). 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 7: Glycemic Parameters at Final Visit (24-Week Trial) for Sitagliptin in Add-on Combination Therapy with Metformin*

	Sitagliptin 100 mg + 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.

Initial Combination Therapy with Metformin

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 as initial therapy in combination with metformin. Patients on an antihyperglycemic agent (N=541) discontinued the agent, and underwent a diet, exercise, and drug washout period of up to 12 weeks duration. After the washout period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized after completing a 2-week single-blind placebo run-in period. Patients not on antihyperglycemic agents at 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 initial therapy with 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.

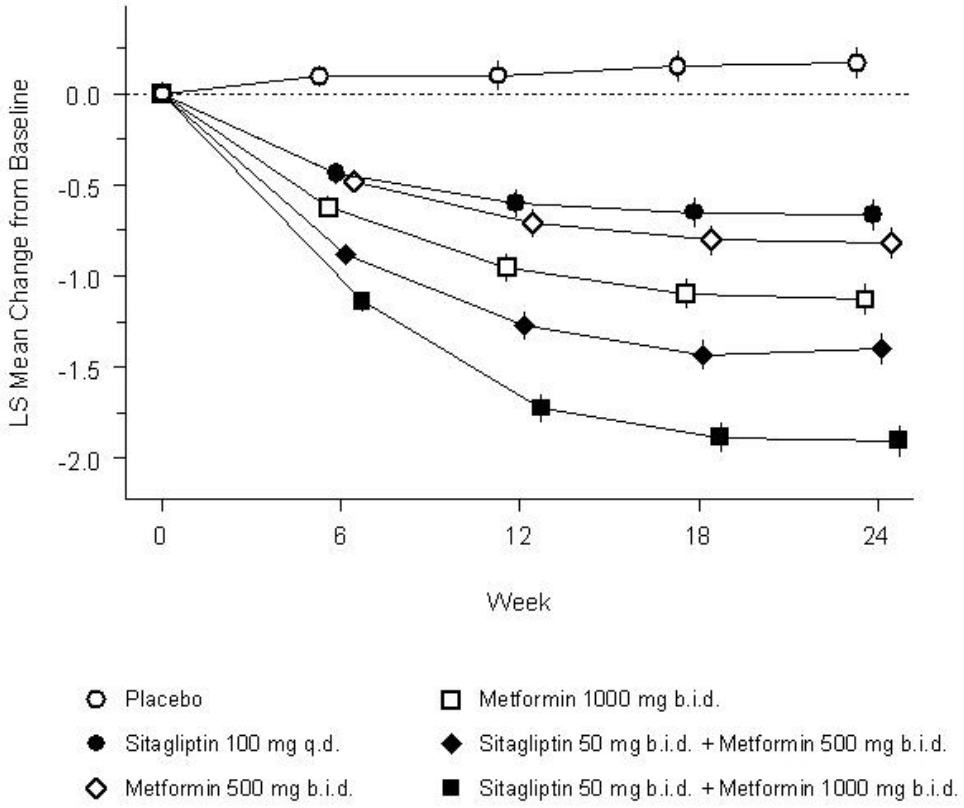
Initial therapy with the combination of sitagliptin and metformin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to sitagliptin alone (Table 8, Figure 1). Mean reductions from baseline in A1C were generally greater for patients with higher baseline 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 8: Glycemic Parameters at Final Visit (24-Week Trial) for Sitagliptin and Metformin, Alone and in Combination as Initial Therapy*

	Placebo	**Sitagliptin 100 mg QD**	**Metformin HCl 500 mg bid**	**Metformin HCl 1,000 mg bid**	**Sitagliptin 50 mg bid + Metformin HCl 500 mg bid**	**Sitagliptin 50 mg bid + Metformin HCl 1,000 mg bid**
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 on 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 as Initial Therapy in Patients with Type 2 Diabetes Mellitus*



*All Patients Treated Population: least squares means adjusted for prior antihyperglycemic therapy and baseline value.

Initial combination therapy or maintenance of combination therapy may not be appropriate for all patients. These management options are left to the discretion of the health care provider.

Active-Controlled Trial vs Glipizide in Combination with 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 HCl 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 9). 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

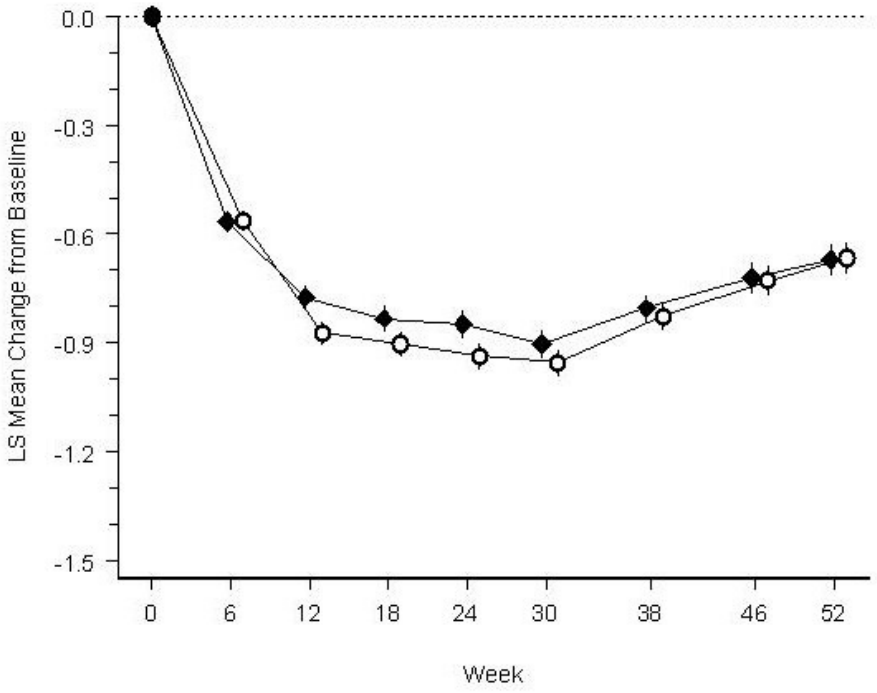
trial (over 70% of patients had baseline A1C <8% and over 90% had A1C <9%).

Table 9: 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	**Glipizide**
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)*



■ Sitagliptin 100 mg ○ Glipizide

*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).

Add-on Combination Therapy with Pioglitazone

A total of 353 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 pioglitazone. Patients on any oral antihyperglycemic agent

in monotherapy (N=212) or on a PPARγ agent in combination therapy (N=106) or not on an antihyperglycemic agent (off therapy for at least 8 weeks, N=34) were switched to monotherapy with pioglitazone (at a dose of 30 to 45 mg per day) and completed a run-in period of approximately 12 weeks in duration. After the run-in period on pioglitazone monotherapy, patients with inadequate glycemic control (A1C 7% to 10%) 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 trials were treated with metformin rescue. Glycemic endpoints measured were A1C and fasting glucose.

In combination with pioglitazone, sitagliptin provided significant improvements in A1C and FPG compared to placebo with pioglitazone (Table 10). Rescue therapy was used in 7% of patients treated with sitagliptin 100 mg and 14% of patients treated with placebo. There was no significant difference between sitagliptin and placebo in body weight change.

Table 10: Glycemic Parameters at Final Visit (24-Week Trial) for Sitagliptin in Add-on Combination Therapy with Pioglitazone*

	Sitagliptin 100 mg + Pioglitazone	**Placebo + Pioglitazone**
A1C (%)	**N = 163**	**N = 174**
Baseline (mean)	8.1	8.0
Change from baseline (adjusted mean†)	-0.9	-0.2
Difference from placebo + pioglitazone (adjusted mean†) (95% CI)	-0.7‡ (-0.9, -0.5)	
Patients (%) achieving A1C <7%	74 (45%)	40 (23%)
FPG (mg/dL)	**N = 163**	**N = 174**
Baseline (mean)	168	166
Change from baseline (adjusted mean†)	-17	1
Difference from placebo + pioglitazone (adjusted mean†) (95% CI)	-18‡ (-24, -11)	

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

Initial Combination Therapy with Pioglitazone

A total of 520 patients with type 2 diabetes mellitus and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind trial designed to assess the efficacy of sitagliptin as initial therapy in combination with pioglitazone. Patients not on antihyperglycemic agents at trial entry (<4 weeks cumulative therapy over the past 2 years, and with no treatment over the prior 4 months) with inadequate glycemic control (A1C 8% to 12%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. Approximately equal numbers of patients were randomized to receive initial therapy with 100 mg of sitagliptin in combination with 30 mg of pioglitazone once daily or 30 mg of pioglitazone once daily as monotherapy. There was no glycemic rescue therapy in this trial.

Initial therapy with the combination of sitagliptin and pioglitazone provided significant improvements in A1C, FPG, and 2-hour PPG compared to pioglitazone monotherapy (Table 11). The improvement in A1C was generally consistent across subgroups defined by gender, age, race, baseline BMI, baseline A1C, or duration of disease. In this trial, patients treated with ZITUVIO in combination with pioglitazone had a mean increase in body weight of 1.1 kg compared to pioglitazone alone (3 kg vs. 1.9 kg). Lipid effects were generally neutral.

Table 11: Glycemic Parameters at Final Visit (24-Week Trial) for Sitagliptin in Combination with Pioglitazone as Initial Therapy*

	Sitagliptin 100 mg + Pioglitazone	**Pioglitazone**
A1C (%)	**N = 251**	**N = 246**

Baseline (mean)	9.5	9.4
Change from baseline (adjusted mean†)	-2.4	-1.5
Difference from pioglitazone (adjusted mean†) (95% CI)	-0.9‡ (-1.1, -0.7)	
Patients (%) achieving A1C <7%	151 (60%)	68 (28%)
FPG (mg/dL)	**N = 256**	**N = 253**
Baseline (mean)	203	201
Change from baseline (adjusted mean†)	-63	-40
Difference from pioglitazone (adjusted mean†) (95% CI)	-23‡ (-30, -15)	
2-hour PPG (mg/dL)	**N = 216**	**N = 211**
Baseline (mean)	283	284
Change from baseline (adjusted mean†)	-114	-69
Difference from pioglitazone (adjusted mean†) (95% CI)	-45‡ (-57, -32)	

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

Add-on Combination Therapy with 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 trial 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 -1.0% for patients treated with sitagliptin and -0.3% for patients treated with placebo in an analysis based on the intent-to-treat population. Rescue therapy was used in 18% of patients treated with sitagliptin 100 mg and 40% of patients treated with placebo. There was no significant difference between sitagliptin and placebo in body weight change.

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

	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 on 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.

Add-on Combination Therapy with Glimepiride, with or without Metformin

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 trials were treated with pioglitazone rescue.

In combination with glimepiride, with or without metformin, sitagliptin provided significant improvements in A1C and FPG compared to placebo (Table 13). In the entire trial population (patients on sitagliptin in combination with glimepiride and patients on sitagliptin in combination with glimepiride and metformin), a mean reduction from baseline relative to placebo in A1C of -0.7% and in FPG of -20 mg/dL was seen. Rescue therapy was used in 12% of patients treated with sitagliptin 100 mg and 27% of patients treated with placebo. In this trial, patients treated with sitagliptin had a mean increase in body weight of 1.1 kg vs. placebo (+0.8 kg vs. -0.4 kg). In addition, there was an increased rate of hypoglycemia. *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)].*

Table 13: Glycemic Parameters at Final Visit (24-Week Trial) for Sitagliptin as Add-On Combination Therapy with Glimepiride, with or without Metformin*

	Sitagliptin 100 mg + Glimepiride	**Placebo + Glimepiride**	**Sitagliptin 100 mg + Glimepiride + Metformin**	**Placebo + Glimepiride + Metformin**
A1C (%)	**N = 102**	**N = 103**	**N = 115**	**N = 105**
Baseline (mean)	8.4	8.5	8.3	8.3
Change from baseline (adjusted mean†)	-0.3	0.3	-0.6	0.3
Difference from placebo (adjusted mean†) (95% CI)	-0.6‡ (-0.8, -0.3)		-0.9‡ (-1.1, -0.7)	
Patients (%) achieving A1C <7%	11 (11%)	9 (9%)	26 (23%)	1 (1%)
FPG (mg/dL)	**N = 104**	**N = 104**	**N = 115**	**N = 109**
Baseline (mean)	183	185	179	179
Change from baseline (adjusted mean†)	-1	18	-8	13
Difference from placebo (adjusted mean†) (95% CI)	-19§ (-32, -7)		-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.
§ p<0.01 compared to placebo.

Add-on Combination Therapy with Insulin (with or without Metformin)

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 (with or without metformin). The racial distribution in this trial was approximately 70% White, 18% Asian, 7% Black or African American, and 5% other groups. Approximately 14% of the patients in this trial were Hispanic or Latino. 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 ZITUVIO or placebo, administered once daily. Patients were on a stable dose of insulin prior to enrolment with no changes in insulin dose permitted during the run-in period. Patients who failed to meet specific glycemic goals during the double-blind treatment period were to have up-titration of the background insulin dose as rescue therapy.

The median daily insulin dose at baseline was 42 units in the patients treated with sitagliptin and 45 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. In combination with insulin (with or without metformin), sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo (Table 14). Both treatment groups had an adjusted mean increase in body weight of 0.1 kg from baseline to Week 24. There was an increased rate of hypoglycemia in patients treated with sitagliptin. *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)].*

Table 14: Glycemic Parameters at Final Visit (24-Week Trial) for Sitagliptin as Add-on Combination Therapy with Insulin*

	Sitagliptin 100 mg + Insulin (+/- Metformin)	**Placebo + Insulin (+/- Metformin)**
A1C (%)	**N = 305**	**N = 312**
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean†)	-0.6	-0.1
Difference from placebo (adjusted mean†,‡) (95% CI)	-0.6§ (-0.7, -0.4)	
Patients (%) achieving A1C <7%	39 (12.8%)	16 (5.1%)
FPG (mg/dL)	**N = 310**	**N = 313**
Baseline (mean)	176	179
Change from baseline (adjusted mean†)	-18	-4
Difference from placebo (adjusted mean†) (95% CI)	-15§ (-23, -7)	
2-hour PPG (mg/dL)	**N = 240**	**N = 257**
Baseline (mean)	291	292
Change from baseline (adjusted mean†)	-31	5
Difference from placebo (adjusted mean†) (95% CI)	-36§ (-47, -25)	

* Intent-to-treat population using last observation on trial prior to rescue therapy.
† Least squares means adjusted for metformin use at the screening visit (yes/no), type of insulin used at the screening visit (pre-mixed vs. non-pre-mixed [intermediate-or long-acting]), and baseline value.
‡ Treatment by stratum interaction was not significant (p>0.10) for metformin stratum and for insulin stratum.
§ 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 mellitus (mean baseline HbA1C 8.8%, disease duration 10.8 years) participated in a 30-week, randomized, double-blind, placebo-controlled trial 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 (≥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 trial. 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 up-titrate 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 15). 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 15: Change from Baseline in A1C and FPG at Week 30 in the Maintenance of Sitagliptin During Initiation and Titration of Insulin Glargine Trial

	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.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZITUVIO are supplied as follows:

Tablet Strength	**Physical Description**	**How Supplied**	**NDC #**
25 mg sitagliptin	White to off white, round, biconvex, film coated tablets debossed with "12" on one side and "40" on the other side	Bottles of 30 tablets with child-resistant closure.	NDC 70771-1770-3
		Bottles of 90 tablets with child-resistant closure.	NDC 70771-1770-9
50 mg sitagliptin	Pale yellow, round, biconvex, film coated tablets debossed with "12" on one side and "41" on the other side	Bottles of 30 tablets with child-resistant closure.	NDC 70771-1771-3
		Bottles of 90 tablets with child-resistant closure.	NDC 70771-1771-9

100 mg sitagliptin	Beige, round, biconvex, film coated tablets debossed with "12" on one side and "42" on the other side	Bottles of 30 tablets with child-resistant closure.	NDC 70771-1772-3
		Bottles of 90 tablets with child-resistant closure.	NDC 70771-1772-9

Storage

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].

Dispense in original container to protect from moisture.

Once the bottle has been opened, the product must be used within 3 months

17 PATIENT COUNSELING INFORMATION

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

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 ZITUVIO and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.1)].*

Heart Failure

Inform patients of the signs and symptoms of heart failure. Before initiating ZITUVIO, 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 (5.2)].*

Hypoglycemia

Inform patients that the incidence of hypoglycemia is increased when sitagliptin is added to a sulfonylurea or insulin. Explain to patients receiving ZITUVIO in combination with these medications the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development *[see Warnings and Precautions (5.4)].*

Hypersensitivity Reactions

Inform patients that allergic reactions have been reported during postmarketing use of sitagliptin. 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 ZITUVIO and seek medical advice promptly. *[see Warnings and Precautions (5.5)].*

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 (5.6)]*.

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 (5.7)].*

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

Manufactured by:

Zydus Lifesciences Ltd.,

Pharmez, Matoda, Ahmedabad, India.

MEDICATION GUIDE

Medication Guide
ZITUVIO (zi too' vee oh)
(sitagliptin)
tablets, for oral use

What is the most important information I should know about ZITUVIO ?
ZITUVIO can cause serious side effects, including:

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 ZITUVIO ,** 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 ZITUVIO 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.

Heart failure . Heart failure means your heart does not pump blood well enough. **Before you start taking ZITUVIO ,** 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 ZITUVIO ?

ZITUVIO is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

ZITUVIO 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 ZITUVIO.

It is not known if ZITUVIO is safe and effective in children.

Do not take ZITUVIO if:

you are allergic to sitagliptin or any of the ingredients in ZITUVIO. See the end of this Medication Guide for a complete list of ingredients in ZITUVIO.
Symptoms of a serious allergic reaction to ZITUVIO may include rash, raised red patches on your skin (hives), or swelling of the face, lips, tongue, and throat that may cause difficulty breathing or swallowing.

Before you take ZITUVIO, 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 heart failure.

are pregnant or plan to become pregnant. It is not known if ZITUVIO 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 ZITUVIO will pass into your breast milk. Talk with your healthcare provider about the best way to feed your baby if you are taking ZITUVIO.

Tell your healthcare provider about all the medicines you take , including prescription and over-the-counter medicines, vitamins, and herbal supplements.
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 ZITUVIO ?

Take ZITUVIO 1 time each day exactly as your healthcare provider tells you.

You can take ZITUVIO with or without food.

Your healthcare provider will do blood tests to check how well your kidneys are working before and during your treatment with ZITUVIO.

Your healthcare provider may tell you to take ZITUVIO along with other diabetes medicines. Low blood sugar can happen more often when ZITUVIO is taken with certain other diabetes medicines. See " **What are the possible side effects of ZITUVIO?** ".

If you take too much ZITUVIO, call your healthcare provider or the 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 ZITUVIO?

ZITUVIO may cause serious side effects, including:

See **"What is the most important information I should know about ZITUVIO?"** .

Kidney problems , sometimes requiring dialysis.

Low blood sugar (hypoglycemia). If you take ZITUVIO 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 ZITUVIO. Signs and symptoms of low blood sugar may include:

- headache
- drowsiness
- irritability
- hunger
- dizziness
- confusion
- sweating
- feeling jittery
- weakness
- fast heartbeat

Serious allergic reactions. If you have any symptoms of a serious allergic reaction, stop taking ZITUVIO and call your healthcare provider right away or get emergency medical help. See " **Do not take ZITUVIO if:** ". 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 ZITUVIO, may develop joint pain that can be severe. Call your healthcare provider if you have severe joint pain.

Skin reaction. Some people who take ZITUVIO 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 ZITUVIO.

The most common side effects of ZITUVIO include upper respiratory infection, stuffy or runny nose and sore throat, and headache.

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

Tell your healthcare provider if you have any side effect that bothers you or does not go away. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZITUVIO?

Store ZITUVIO in the original container at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ZITUVIO in the original container to protect it from moisture

Use ZITUVIO within 3 months of opening the bottle

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

General information about the safe and effective use of ZITUVIO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ZITUVIO for a condition for which it was not prescribed. Do not give ZITUVIO to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about ZITUVIO that is written for health professionals.

What are the ingredients in ZITUVIO?

Active ingredient: sitagliptin

Inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide,

croscarmellose sodium, malic acid, magnesium stearate, microcrystalline cellulose, and povidone. In addition, the film coating contains the following inactive ingredients: polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The 50 mg tablet's film coating also contains ferrosoferric oxide and iron oxide yellow. The 100 mg tablet's film coating also contains FD&C Yellow #6 Aluminum Lake and iron oxide yellow.

Manufactured by: Zydus Lifesciences Ltd., Pharmez, Matoda, Ahmedabad, India

The trademarks depicted herein are owned by their respective companies.

Please address medical inquiries to, (MedicalAffairs@zydususa.com) 1-877-993-8779.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Issued: 10/2023

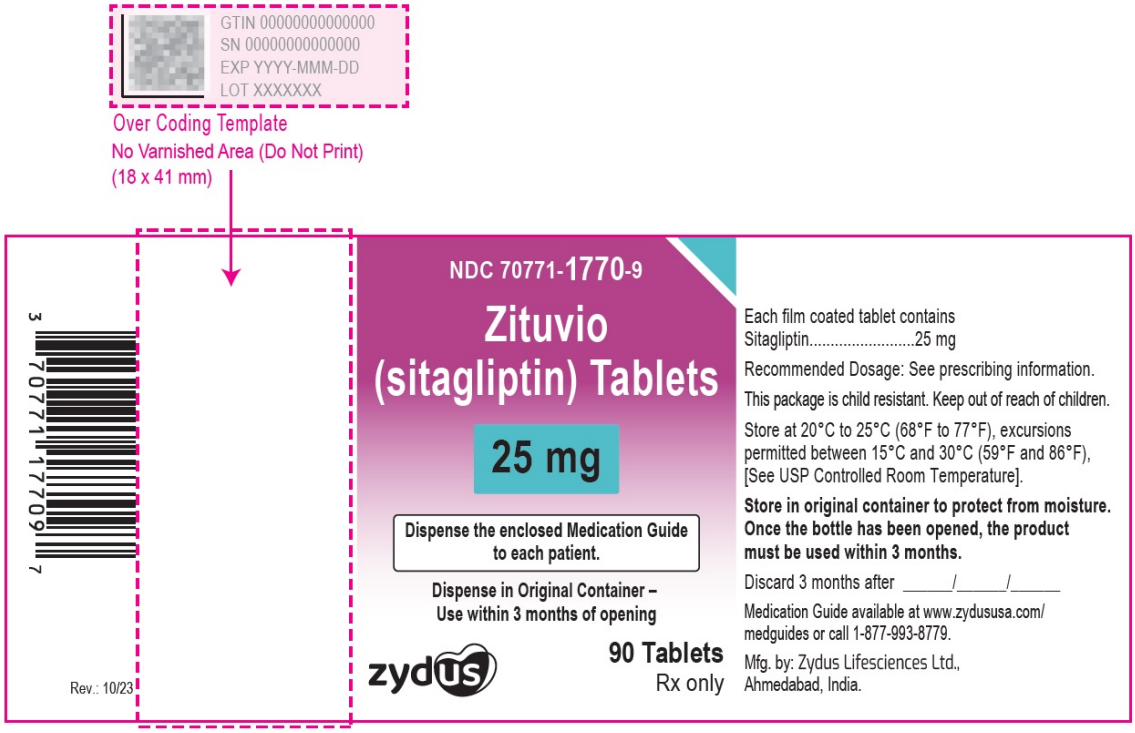
PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 70771-1770-9 in bottles of 90 tablets

Zituvio (sitagliptin) Tablets, 25 mg

90 Tablets

Rx Only

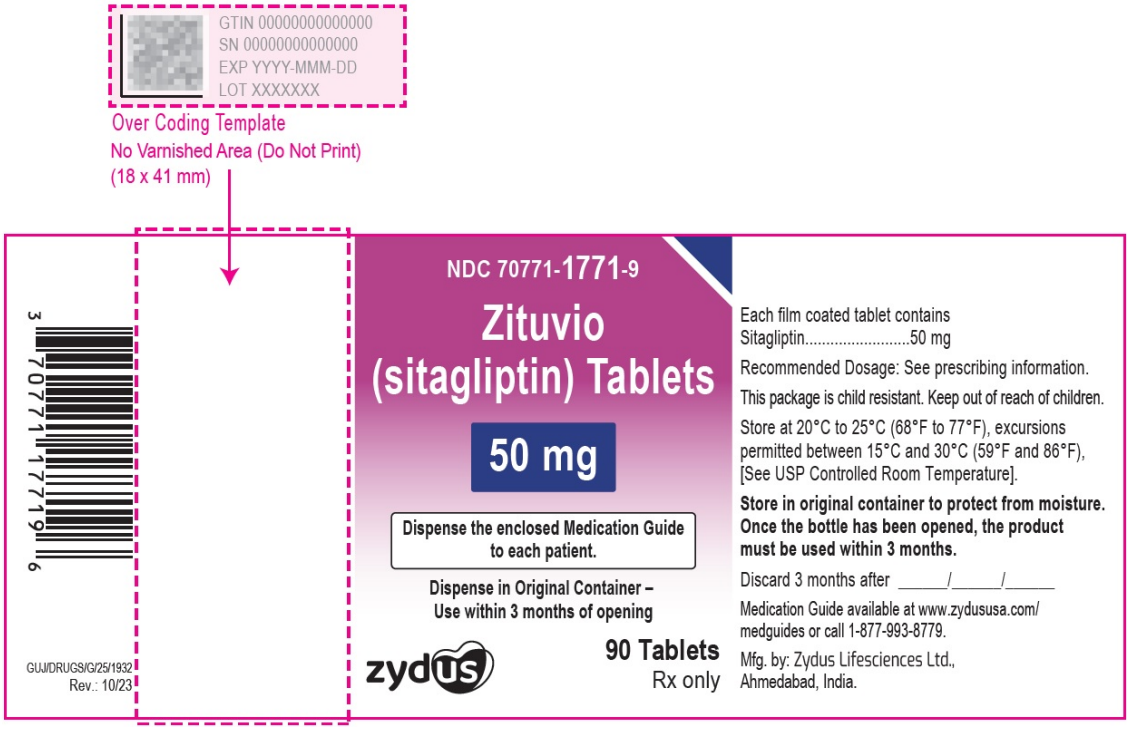


NDC 70771-1771-9 in bottles of 90 tablets

Zituvio (sitagliptin) Tablets, 50 mg

90 Tablets

Rx Only

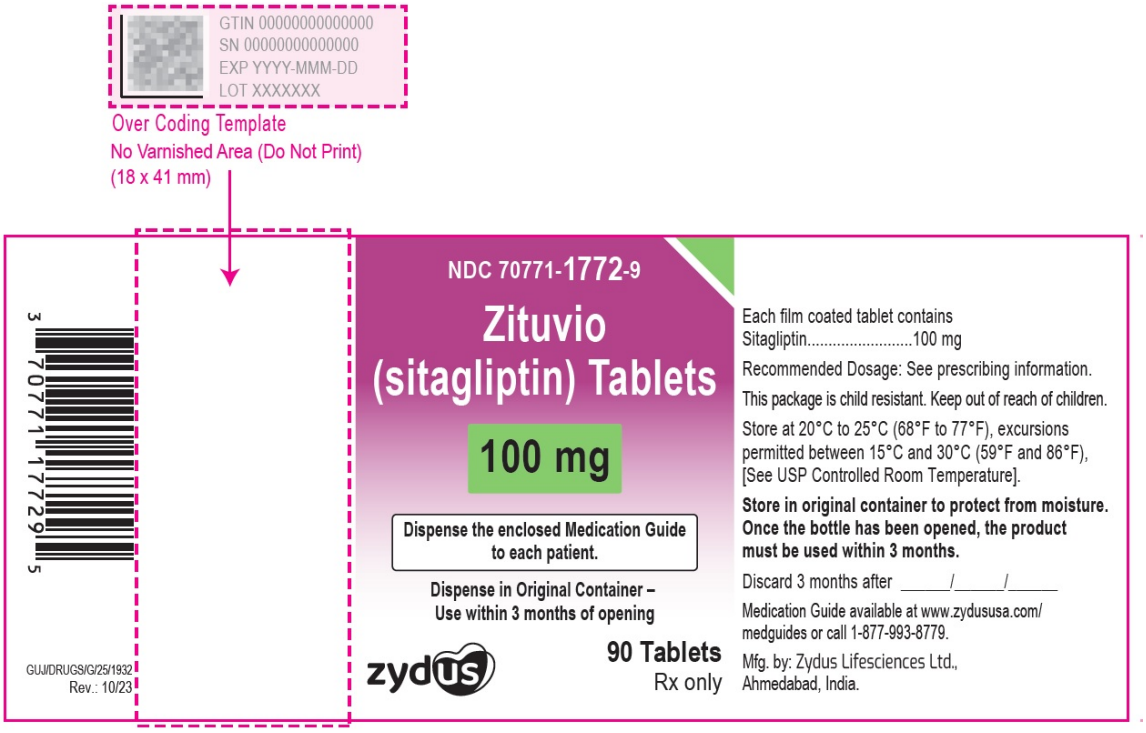


NDC 70771-1772-9 in bottles of 90 tablets

Zituvio (sitagliptin) Tablets, 100 mg

90 Tablets

Rx Only



ZITUVIO
sitagliptin tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70771-1770
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SITAGLIPTIN (UNII: QFP0P1DV7Z) (SITAGLIPTIN - UNII:QFP0P1DV7Z)	SITAGLIPTIN	25 mg

Inactive Ingredients

Ingredient Name	Strength
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MALIC ACID (UNII: 817L1N4CKP)	
POLYETHYLENE GLYCOL 3350 (UNII: G2M7P15E5P)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
ANHYDROUS DIBASIC CALCIUM PHOSPHATE (UNII: L11K75P92J)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	WHITE (white to off-white)	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	12;40
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70771-1770-3	30 in 1 BOTTLE; Type 0: Not a Combination Product	11/30/2023	
2	NDC:70771-1770-9	90 in 1 BOTTLE; Type 0: Not a Combination Product	11/30/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA211566	11/30/2023	

ZITUVIO

sitagliptin tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70771-1771
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SITAGLIPTIN (UNII: QFP0P1DV7Z) (SITAGLIPTIN - UNII:QFP0P1DV7Z)	SITAGLIPTIN	50 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS DIBASIC CALCIUM PHOSPHATE (UNII: L11K75P92J)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 3350 (UNII: G2M7P15E5P)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
MALIC ACID (UNII: 817L1N4CKP)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics

Color	YELLOW (pale yellow)	**Score**	no score
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	12;41
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70771-1771-3	30 in 1 BOTTLE; Type 0: Not a Combination Product	11/30/2023	
2	NDC:70771-1771-9	90 in 1 BOTTLE; Type 0: Not a Combination Product	11/30/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA211566	11/30/2023	

ZITUVIO

sitagliptin tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70771-1772
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SITAGLIPTIN (UNII: QFP0P1DV7Z) (SITAGLIPTIN - UNII:QFP0P1DV7Z)	SITAGLIPTIN	100 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS DIBASIC CALCIUM PHOSPHATE (UNII: L11K75P92J)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 3350 (UNII: G2M7P15E5P)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
MALIC ACID (UNII: 817L1N4CKP)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics

Color	BROWN (beige)	**Score**	no score
Shape	ROUND	**Size**	10mm
Flavor		**Imprint Code**	12;42
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70771-1772-3	30 in 1 BOTTLE; Type 0: Not a Combination Product	11/30/2023	
2	NDC:70771-1772-9	90 in 1 BOTTLE; Type 0: Not a Combination Product	11/30/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA211566	11/30/2023	

Labeler - Zydus Lifesciences Limited (918596198)

Registrant - Zydus Worldwide DMCC (557951127)

Establishment

Name	Address	ID/FEI	Business Operations
Zydus Lifesciences Limited		918596198	ANALYSIS(70771-1770, 70771-1771, 70771-1772) , MANUFACTURE(70771-1770, 70771-1771, 70771-1772)

Revised: 11/2023 Zydus Lifesciences Limited