PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]PRZ-SITAGLIPTIN

Sitagliptin (as sitagliptin phosphate monohydrate)
Tablets, 25, 50 and 100 mg, Oral

USP

Dipeptidyl peptidase 4 (DPP-4) inhibitors

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RECENT MAJOR LABEL CHANGES

Not Applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

- **Monotherapy**: PRZ-SITAGLIPTIN (sitagliptin) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.

- **Add-on combination**: PRZ-SITAGLIPTIN is indicated in adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with:

  . metformin,
  . metformin and a sulfonylurea,
  . pioglitazone (alone or with metformin),
  . premixed or long/intermediate acting insulin (alone or with metformin)

  when the existing therapy, along with diet and exercise, does not provide adequate glycemic control (see 14 CLINICAL TRIALS).

1.1 Pediatrics

- **Pediatrics (<18 years of age):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of sitagliptin in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

- **Geriatrics (≥65 years of age):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of sitagliptin in geriatric patients has been established. Therefore, Health Canada has authorized an indication for geriatric use (see 7 WARNINGS AND PRECAUTIONS, 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

2 CONTRAINDICATIONS

- Patients with a history of a hypersensitive reaction to PRZ-SITAGLIPTIN or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS). For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **Concomitant Use with Insulin or an Insulin Secretagogue (e.g., Sulfonylurea)**
  When PRZ-SITAGLIPTIN is used in combination with metformin and a sulfonylurea or with insulin (with or without metformin), a lower dose of the insulin secretagogue or insulin may be considered to reduce the risk of hypoglycemia (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of PRZ-SITAGLIPTIN is **100 mg** once daily as monotherapy or as combination therapy with metformin, with metformin and a sulfonylurea, with insulin (with or without metformin), or with pioglitazone (with or without metformin).

Renal Impairment: Sitagliptin is renally excreted. Renal function must be assessed prior to initiation of PRZ-SITAGLIPTIN and periodically thereafter because, there is a dosage adjustment based upon renal function (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Severe renal impairment: For patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or with end-stage renal disease (ESRD) including those requiring hemodialysis or peritoneal dialysis, the dose of PRZ-SITAGLIPTIN is **25 mg** once daily. PRZ-SITAGLIPTIN may be administered without regard to the timing of dialysis.

Moderate renal impairment: For patients with moderate renal impairment with an eGFR 30 mL/min/1.73 m^2 to less than 45 mL/min/1.73 m^2, the dose of PRZ-SITAGLIPTIN is **50 mg** once daily.

No dosage adjustment for PRZ-SITAGLIPTIN is required in patients with moderate renal impairment with an eGFR ≥45 mL/min/1.73 m^2 to less than 60 mL/min/1.73 m^2.

Mild renal impairment: No dosage adjustment for PRZ-SITAGLIPTIN is required in patients with mild renal impairment (eGFR 60 mL/min/1.73 m^2 to <90 mL/min/1.73 m^2).

When considering the use of sitagliptin in combination with another anti-diabetic product, its conditions for use in patients with renal impairment should be followed.

Hepatic Impairment: No dosage adjustment of PRZ-SITAGLIPTIN is necessary in patients with mild or moderate hepatic impairment. Sitagliptin has not been studied in patients with severe hepatic impairment and is not recommended for use in this population.

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): No dosage adjustment is necessary for geriatric patients. However, 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 7 WARNINGS AND PRECAUTIONS, Special Populations).

4.4 Administration

PRZ-SITAGLIPTIN can be taken with or without food

4.5 Missed Dose

If a dose of PRZ-SITAGLIPTIN is missed, it should be taken as soon as the patient remembers. A double dose of PRZ-SITAGLIPTIN should not be taken on the same day.

5 OVERDOSAGE

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	**Tablets:** sitagliptin (as sitagliptin phosphate monohydrate) 25 mg[1] 50 mg[2] 100 mg[3]	Calcium hydrogen phosphate, croscarmellose sodium, instacoat pink (for 25 mg), instacoat beige (for 50 mg), instacoat peach (for 100 mg), purified water, microcrystalline cellulose, and sodium stearyl fumerate

[1] 32.10 mg of sitagliptin phosphate monohydrate

[2] 64.24 mg of sitagliptin phosphate monohydrate

[3] 128.48 mg of sitagliptin phosphate monohydrate

Tablets PRZ-SITAGLIPTIN, 25 mg, are pink, round shaped, film-coated tablets with “S1” on one side and plain on other side. They are supplied in blister packs of 1x10s, and bottles of 30s and 100s.

Tablets PRZ-SITAGLIPTIN, 50 mg, are light beige, round shaped, film-coated tablets with "S2" on one side and plain on other side. They are supplied in blister packs of 1x10s, and bottles of 30s and 100s.

Tablets PRZ-SITAGLIPTIN, 100 mg, are beige, round shaped, film-coated tablets with "S3" on one side and plain on other side. They are supplied in blister packs of 1x10s, and bottles of 100s.

7 WARNINGS AND PRECAUTIONS

General

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

Driving and Operating Machinery

Patients should be warned about driving or operating a vehicle or potentially dangerous machinery under conditions where a risk of hypoglycemia is present. When PRZ-SITAGLIPTIN is used in combination with metformin and a sulfonylurea, or in combination with insulin (with or without metformin), patients should be advised to take precautions to avoid hypoglycemia while driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Hypoglycemia: When sitagliptin was used in combination with metformin and a sulfonylurea, or with a stable dose of insulin (with or without metformin), the incidence of hypoglycemia was increased over that of placebo used in combination with metformin and a sulfonylurea or in combination with insulin (with or without metformin) (see 8 ADVERSE REACTIONS). To reduce the risk of hypoglycemia associated with these indications, a lower dose of sulfonylurea or insulin may be considered (see 4 DOSAGE AND ADMINISTRATION).

Loss of Control of Blood Glucose: The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with PRZ-SITAGLIPTIN, therapeutic alternatives should be considered.

Hepatic/Biliary/Pancreatic

Hepatic: There are limited clinical experiences in patients with moderate hepatic impairment and no clinical experience in patients with severe hepatic impairment. Use in patients with severe hepatic impairment is not recommended (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

Pancreatitis: There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin. In a long-term cardiovascular outcomes trial (see 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS), there were two adjudication-confirmed deaths due to acute pancreatitis in patients treated with sitagliptin compared to none in the placebo group. After initiation of PRZ-SITAGLIPTIN, patients should be observed carefully

for signs and symptoms of pancreatitis. If pancreatitis is suspected, PRZ-SITAGLIPTIN should promptly be discontinued and appropriate management should be initiated. Risk factors for pancreatitis include a history of: pancreatitis, gallstones, alcoholism, or hypertriglyceridemia.

Immune

Hypersensitivity Reactions: There have been post-marketing 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 PRZ-SITAGLIPTIN, assess for other potential causes for the event, and institute alternative treatment for diabetes (see 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS).

Immunocompromised Patients: A dose-related mean decrease in absolute lymphocyte count was observed with other members of this class. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of sitagliptin on lymphocyte counts in patients with lymphocyte abnormalities (e.g. human immunodeficiency virus) is unknown.
Immunocompromised patients, such as patients who have undergone organ transplantation or patients diagnosed with human immunodeficiency syndrome have not been studied in the sitagliptin clinical program. Therefore, the efficacy and safety profile of sitagliptin in these patients has not been established.

Monitoring and Laboratory Tests

Blood Glucose and HbA_{1c}: Response to PRZ-SITAGLIPTIN should be monitored by periodic measurements of blood glucose and HbA_{1c} levels.

Renal Function: Renal function must be assessed prior to initiation of PRZ-SITAGLIPTIN and periodically thereafter as lower dosages are recommended in patients whose estimated glomerular rate (eGFR) decreases to less than 45 mL/min/1.73 m^2 as well as in patients with severe renal impairment and in patients with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis (see 4 DOSAGE AND ADMINISTRATION).

Monitoring of renal function is recommended prior to and following initiation of any concomitant drug which might have an impact on renal function.

Renal

Renal-related adverse events, including acute renal failure, have been observed during clinical trials and post-marketing use of sitagliptin in patients with and without known risk factors (see 8 ADVERSE REACTIONS).

Renal function must be assessed prior to initiation of PRZ-SITAGLIPTIN and periodically thereafter. Since sitagliptin is renally excreted and sitagliptin exposure is increased in patients with renal impairment, a dose adjustment of PRZ-SITAGLIPTIN is required in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2 (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, 4 DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY). Caution should be used to ensure that the correct dose of PRZ-SITAGLIPTIN is prescribed for patients with moderate (eGFR ≥30 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2) or severe (eGFR <30 mL/min/1.73 m^2) renal impairment, as well as in patients with ESRD requiring

hemodialysis or peritoneal dialysis (see 4 DOSAGE AND ADMINISTRATION).

Skin

With other members of this class, ulcerative and necrotic skin lesions have been reported in monkeys in non-clinical toxicology studies. There is limited experience in patients with diabetic skin complications. In keeping with routine care of the diabetic patient, monitoring for skin disorders is recommended.

Bullous Pemphigoid: Post-marketing cases of bullous pemphigoid requiring hospitalization have been reported with the use of dipeptidyl peptidase 4 (DPP-4) inhibitors, including sitagliptin. 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 PRZ-SITAGLIPTIN. If bullous pemphigoid is suspected, PRZ-SITAGLIPTIN should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Reproductive Health: Female and Male Potential

See 7.1.1 SPECIAL POPULATIONS, Pregnant Women

7.1 Special Populations

7.1.1 Pregnant Women

PRZ-SITAGLIPTIN is not recommended for use in pregnancy. There are very limited data for the use of sitagliptin in pregnant women in clinical studies, including no adequate and well-controlled studies in this population; therefore, the safety of PRZ-SITAGLIPTIN in pregnant women is not known.

The extent of exposure in pregnancy during clinical trials: Very limited.

7.1.2 Breast-feeding

Sitagliptin is secreted in the milk of lactating rats. It is unknown if sitagliptin is excreted in human milk. Therefore, PRZ-SITAGLIPTIN should not be used by a woman during breastfeeding.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of sitagliptin in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): In clinical studies, no overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the geriatric and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Because sitagliptin is excreted by the kidney and geriatric patients are more likely to have decreased renal function, care should be taken in dose selection and should be based on careful and regular monitoring of renal function (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL

PHARMACOLOGY).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Sitagliptin was generally well tolerated in controlled clinical studies as monotherapy and as part of combination therapy with metformin or combination therapy with metformin and a sulfonylurea agent, or add-on combination therapy with insulin (with or without metformin) or as add-on combination therapy with pioglitazone (with or without metformin).

The incidences of serious adverse reactions and discontinuation of therapy due to clinical adverse reactions were generally similar to placebo. The most frequent adverse events in trials of sitagliptin as monotherapy (placebo-controlled) and as add-on combination therapy with metformin (reported regardless of causality and more common with sitagliptin than other treatments) was nasopharyngitis. The most frequent adverse events with sitagliptin as add-on combination therapy with metformin and a sulfonylurea agent, or as add-on combination therapy with insulin (with or without metformin), was hypoglycemia.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Monotherapy:
Two placebo-controlled monotherapy studies, one of 18- and one of 24-week duration, included patients treated with sitagliptin 100 mg once daily and patients given placebo. Adverse events reported regardless of causality assessment, in ≥1% of patients in these two studies pooled are shown in Table 2.

Table 2 – Adverse Events ≥1% in Any Treatment Group (regardless of causality) Reported in Patients Treated with sitagliptin 100 mg or Placebo in Pooled 18 and 24-Week Placebo-Controlled, Double-Blind Clinical Trials of sitagliptin as Monotherapy

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg n=443**	**Placebo n=363**
Eye disorders		
Conjunctivitis	3 (0.7)	4 (1.1)
Gastrointestinal disorders		
Abdominal pain	5 (1.1)	6 (1.7)
Constipation	13 (2.9)	5 (1.4)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg n=443**	**Placebo n=363**
Diarrhea	19 (4.3)	10 (2.8)
Gastritis	2 (0.5)	4 (1.1)
Nausea	7 (1.6)	3 (0.8)
Vomiting	3 (0.7)	4 (1.1)
General disorders and administration site conditions		
Fatigue	5 (1.1)	9 (2.5)
Edema peripheral	7 (1.6)	4 (1.1)
Pain	0 (0.0)	4 (1.1)
Infections and infestations		
Bronchitis	5 (1.1)	6 (1.7)
Gastroenteritis	6 (1.4)	4 (1.1)
Influenza	19 (4.3)	16 (4.4)
Nasopharyngitis	23 (5.2)	12 (3.3)
Pharyngitis	5 (1.1)	1 (0.3)
Sinusitis	6 (1.4)	9 (2.5)
Upper respiratory tract infection	29 (6.5)	24 (6.6)
Urinary tract infection	8 (1.8)	9 (2.5)
Viral infection	2 (0.5)	4 (1.1)
Viral upper respiratory tract infection	5 (1.1)	1 (0.3)
Injury, poisoning and procedural complications		
Limb injury	3 (0.7)	4 (1.1)
Investigations		
Blood glucose increased	7 (1.6)	13 (3.6)
Metabolism and nutrition disorders		
Hyperglycemia	5 (1.1)	7 (1.9)
Hypoglycemia	5 (1.1)	2 (0.6)
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (0.9)	9 (2.5)
Back pain	14 (3.2)	12 (3.3)
Muscle spasm	6 (1.4)	4 (1.1)
Myalgia	6 (1.4)	4 (1.1)
Neck pain	1 (0.2)	4 (1.1)
Osteoarthritis	5 (1.1)	1 (0.3)
Pain in extremity	7 (1.6)	6 (1.7)
Nervous system disorders		

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg n=443**	**Placebo n=363**
Dizziness	7 (1.6)	8 (2.2)
Headache	18 (4.1)	14 (3.9)
Paresthesia	4 (0.9)	4 (1.1)
Psychiatric disorders		
Anxiety	3 (0.7)	4 (1.1)
Insomnia	4 (0.9)	6 (1.7)
Respiratory, thoracic and mediastinal disorders		
Cough	8 (1.8)	10 (2.8)
Vascular disorders		
Hypertension	8 (1.8)	7 (1.9)

In a 24-week study which compared sitagliptin and metformin, adverse events, reported regardless of causality assessment, in ≥1% of patients are shown in Table 3.

Table 3 – Adverse Events ≥1% in Any Treatment Group (regardless of causality) Reported in Patients in 24-Week Active-Controlled, Double-Blind Clinical Trial of sitagliptin as Monotherapy

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg n=528**	**Metformi n n=522**
Gastrointestinal disorders		
Abdominal pain	4 (0.8)	6 (1.1)
Abdominal pain upper	5 (0.9)	12 (2.3)
Constipation	9 (1.7)	5 (1.0)
Diarrhea	19 (3.6)	57 (10.9)
Dyspepsia	1 (0.2)	7 (1.3)
Gastritis	6 (1.1)	11 (2.1)
Nausea	6 (1.1)	16 (3.1)
Vomiting	2 (0.4)	7 (1.3)
General disorders and administration site conditions		
Fatigue	6 (1.1)	6 (1.1)
Infections and infestations		
Bronchitis	4 (0.8)	7 (1.3)
Influenza	12 (2.3)	11 (2.1)
Nasopharyngitis	10 (1.9)	17 (3.3)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg n=528**	**Metformin n n=522**
Upper respiratory tract infection	5 (0.9)	11 (2.1)
Urinary tract infection	3 (0.6)	13 (2.5)
Metabolism and nutrition disorders		
Hypoglycemia	9 (1.7)	18 (3.4)
Musculoskeletal and connective tissue disorders		
Back pain	9 (1.7)	9 (1.7)
Pain in extremity	7 (1.3)	2 (0.4)
Nervous system disorders		
Dizziness	9 (1.7)	5 (1.0)
Headache	17 (3.2)	17 (3.3)
Respiratory, thoracic and mediastinal disorders		
Cough	1 (0.2)	8 (1.5)
Vascular disorders		
Hypertension	12 (2.3)	4 (0.8)

In two monotherapy studies, diarrhea was the only drug-related adverse reaction reported by the investigator that occurred with an incidence ≥1% in patients receiving sitagliptin 100 mg (1.1%) and greater than in patients receiving placebo (0.3%).

Combination Therapy – Sitagliptin Add-on to metformin:
In a 24-week placebo-controlled clinical study of patients receiving sitagliptin (100 mg daily) as add-on combination therapy with metformin the incidence of adverse events reported regardless of causality assessment, in ≥1% of patients are shown in Table 4.

Table 4 – Adverse Events ≥1% in Any treatment Group (regardless of causality) Reported in Patients in a 24- week Placebo-Controlled, Double-Blind Clinical Trial of sitagliptin in Add-on Combination Use with Metformin

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin n=464**	**Placebo + Metformin n=237**
Ear and labyrinth disorders		
Vertigo	5 (1.1)	4 (1.7)
Eye disorders		
Vision blurred	1 (0.2)	3 (1.3)
Gastrointestinal disorders		
Abdominal pain	2 (0.4)	6 (2.5)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin n=464**	**Placebo + Metformin n=237**
Abdominal pain upper	6 (1.3)	2 (0.8)
Constipation	5 (1.1)	1 (0.4)
Diarrhea	11 (2.4)	6 (2.5)
Nausea	6 (1.3)	2 (0.8)
Vomiting	5 (1.1)	2 (0.8)
General disorders and administration site conditions		
Fatigue	2 (0.4)	4 (1.7)
Edema peripheral	4 (0.9)	3 (1.3)
Infections and infestations		
Bronchitis	12 (2.6)	6 (2.5)
Bronchitis acute	2 (0.4)	3 (1.3)
Gastroenteritis	4 (0.9)	5 (2.1)
Influenza	19 (4.1)	12 (5.1)
Nasopharyngitis	19 (4.1)	7 (3.0)
Pharyngitis	6 (1.3)	1 (0.4)
Infections and infestations		
Pneumonia	5 (1.1)	0 (0.0)
Sinusitis	7 (1.5)	2 (0.8)
Tooth infection	5 (1.1)	2 (0.8)
Upper respiratory tract infection	34 (7.3)	22 (9.3)
Urinary tract infection	9 (1.9)	2 (0.8)
Injury, poisoning and procedural complications		
Contusion	5 (1.1)	1 (0.4)
Investigations		
Blood glucose increased	3 (0.6)	6 (2.5)
Metabolism and nutrition disorders		
Hyperglycemia	2 (0.4)	7 (3.0)
Hypoglycemia	6 (1.3)	5 (2.1)
Musculoskeletal and connective tissue disorders		
Arthralgia	14 (3.0)	1 (0.4)
Back pain	15 (3.2)	6 (2.5)
Muscle spasm	1 (0.2)	3 (1.3)
Myalgia	1 (0.2)	3 (1.3)
Pain in extremity	5 (1.1)	4 (1.7)
Shoulder pain	3 (0.6)	3 (1.3)
Nervous system disorders		

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin n=464**	**Placebo + Metformin n=237**
Dizziness	7 (1.5)	2 (0.8)
Headache	12 (2.6)	7 (3.0)
Sciatica	1 (0.2)	3 (1.3)
Sinus headache	0 (0.0)	3 (1.3)
Psychiatric disorders		
Insomnia	5 (1.1)	3 (1.3)
Renal and urinary disorders		
Nephrolithiasis	3 (0.6)	3 (1.3)
Respiratory, thoracic and mediastinal disorders		
Cough	14 (3.0)	4 (1.7)
Vascular disorders		
Hypertension	7 (1.5)	6 (2.5)

In a combination therapy study with metformin, nausea was the only drug-related adverse reaction reported by the investigator that occurred with an incidence ≥1% in patients receiving sitagliptin (1.1%) and greater than in patients receiving placebo (0.4%).

In pooled studies of up to one year duration which compared sitagliptin added to metformin or a sulfonylurea agent (glipizide) added to metformin, adverse events, reported regardless of causality assessment, in ≥1% of patients are shown in Table 5.

Table 5 – Adverse Events ≥1% in Any Treatment Group (regardless of causality) Reported in Patients from Double-Blind Clinical Trials of sitagliptin in Add-on Combination Use with Metformin in Studies Up to One Year Compared to a Sulfonylurea Agent (Glipizide)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin n=979**	**Glipizide + Metformin n=748**
Gastrointestinal disorders		
Abdominal pain	10 (1.0)	6 (0.8)
Abdominal pain upper	13 (1.3)	7 (0.9)
Constipation	17 (1.7)	13 (1.7)
Diarrhea	42 (4.3)	36 (4.8)
Dyspepsia	14 (1.4)	12 (1.6)
Nausea	19 (1.9)	16 (2.1)
Toothache	2 (0.2)	13 (1.7)
Vomiting	11 (1.1)	9 (1.2)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin n=979**	**Glipizide + Metformin n=748**
General disorders and administration site conditions		
Fatigue	20 (2.0)	8 (1.1)
Non-cardiac chest pain	10 (1.0)	6 (0.8)
Edema peripheral	16 (1.6)	14 (1.9)
Infections and infestations		
Bronchitis	27 (2.8)	22 (2.9)
Cellulitis	7 (0.7)	10 (1.3)
Gastroenteritis	19 (1.9)	13 (1.7)
Gastroenteritis viral	8 (0.8)	9 (1.2)
Herpes zoster	4 (0.4)	8 (1.1)
Influenza	35 (3.6)	32 (4.3)
Nasopharyngitis	75 (7.7)	49 (6.6)
Sinusitis	20 (2.0)	12 (1.6)
Upper respiratory tract infection	78 (8.0)	70 (9.4)
Urinary tract infection	41 (4.2)	21 (2.8)
Investigations		
Blood glucose decreased	5 (0.5)	16 (2.1)
Blood glucose increased	13 (1.3)	5 (0.7)
Weight increased	1 (0.1)	8 (1.1)
Metabolism and nutrition disorders		
Hyperglycemia	10 (1.0)	6 (0.8)
Hypoglycemia	32 (3.3)	217 (29.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	34 (3.5)	29 (3.9)
Back pain	39 (4.0)	32 (4.3)
Muscle spasms	9 (0.9)	8 (1.1)
Neck pain	4 (0.4)	8 (1.1)
Osteoarthritis	18 (1.8)	5 (0.7)
Pain in extremity	23 (2.3)	9 (1.2)
Shoulder pain	7 (0.7)	14 (1.9)
Nervous system disorders		
Dizziness	26 (2.7)	14 (1.9)
Headache	34 (3.5)	31 (4.1)
Hypoaesthesia	3 (0.3)	11 (1.5)
Psychiatric disorders		
Anxiety	13 (1.3)	7 (0.9)
Depression	10 (1.0)	7 (0.9)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin n=979**	**Glipizide + Metformin n=748**
Insomnia	12 (1.2)	11 (1.5)
Reproductive system and breast disorders		
Erectile dysfunction	6 (0.6)	8 (1.1)
Respiratory, thoracic and mediastinal disorders		
Cough	19 (1.9)	23 (3.1)
Pharyngolaryngeal pain	10 (1.0)	9 (1.2)
Sinus congestion	5 (0.5)	8 (1.1)
Eczema	4 (0.4)	12 (1.6)
Vascular disorders		
Hypertension	33 (3.4)	29 (3.9)

Combination Therapy: Sitagliptin Add-on to Metformin and a Sulfonylurea

In a 24-week placebo-controlled study of sitagliptin 100 mg in combination with metformin and glimepiride (sitagliptin, N=116; placebo, N=113), the incidence of adverse events, reported regardless of causality assessment, in ≥1% of patients are shown in Table 6. The overall incidence of adverse events with sitagliptin was higher than with placebo, in part related to higher incidence of hypoglycemia (see Table 6).

Table 6 – Adverse Events ≥1% in Any Treatment Group (regardless of causality) Reported in Patients in a 24- Week Placebo-Controlled, Double-Blind Clinical Trial of sitagliptin in Add-on Combination Use with Metformin and a Sulfonylurea Agent (Glimepiride)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Glimepiride n=116**	**Placebo + Metformin + Glimepiride n=113**
Ear and Labyrinth Disorders		
Vertigo	2 (1.7)	0 (0.0)
Eye Disorders		
Diabetic retinopathy	0 (0.0)	2 (1.8)
Vision blurred	0 (0.0)	2 (1.8)
Gastrointestinal disorders		
Abdominal pain upper	2 (1.7)	2 (1.8)
Constipation	4 (3.4)	0 (0.0)
Diarrhea	1 (0.9)	4 (3.5)
Dyspepsia	3 (2.6)	2 (1.8)
Gastritis	0 (0.0)	4 (3.5)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Glimepiride n=116**	**Placebo + Metformin + Glimepiride n=113**
Toothache	2 (1.7)	2 (1.8)
Vomiting	2 (1.7)	1 (0.9)
General disorders and administration site conditions		
Fatigue	0 (0.0)	3 (2.7)
Non-Cardiac chest pain	2 (1.7)	1 (0.9)
Pyrexia	0 (0.0)	2 (1.8)
Hepatobiliary disorders		
Cholelithiasis	0 (0.0)	2 (1.8)
Infections and infestations		
Bronchitis	2 (1.7)	2 (1.8)
Gastroenteritis	3 (2.6)	0 (0.0)
Gastroenteritis viral	2 (1.7)	2 (1.8)
Influenza	3 (2.6)	2 (1.8)
Nasopharyngitis	7 (6.0)	9 (8.0)
Pharyngitis	1 (0.9)	3 (2.7)
Pneumonia	3 (2.6)	0 (0.0)
Rhinitis	2 (1.7)	0 (0.0)
Sinusitis	1 (0.9)	2 (1.8)
Tooth abscess	2 (1.7)	1 (0.9)
Upper respiratory tract infection	8 (6.9)	9 (8.0)
Urinary tract infection	2 (1.7)	1 (0.9)
Injury, poisoning and procedural complications		
Fall	0 (0.0)	3 (2.7)
Polytraumatism	1 (0.9)	2 (1.8)
Investigations		
Blood glucose decreased	0 (0.0)	2 (1.8)
Metabolism and nutrition disorders		
Hypoglycemia	19 (16.4)	1 (0.9)
Musculoskeletal and connective tissue disorders		
Arthralgia	5 (4.3)	1 (0.9)
Back pain	1 (0.9)	2 (1.8)
Muscle spasms	2 (1.7)	1 (0.9)
Osteoarthritis	2 (1.7)	0 (0.0)
Pain in extremity	4 (3.4)	1 (0.9)
Shoulder pain	0 (0.0)	2 (1.8)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Glimepiride n=116**	**Placebo + Metformin + Glimepiride n=113**
Nervous system disorders		
Dizziness	3 (2.6)	1 (0.9)
Headache	8 (6.9)	3 (2.7)
Hypoaesthesia	2 (1.7)	0 (0.0)
Somnolence	0 (0.0)	2 (1.8)
Respiratory, thoracic and mediastinal disorders		
Asthma	2 (1.7)	1 (0.9)
Skin and subcutaneous tissue disorders		
Pruritus	2 (1.7)	1 (0.9)
Rash	2 (1.7)	1 (0.9)
Vascular disorders		
Hypertension	2 (1.7)	0 (0.0)

In a combination therapy study with metformin and a sulfonylurea, hypoglycemia (sitagliptin 13.8%; placebo 0.9%) and constipation (sitagliptin 1.7%; placebo 0.0%) were the only drug-related adverse reactions reported by the investigator that occurred with an incidence ≥1% in patients receiving sitagliptin and metformin and a sulfonylurea and greater than in patients receiving placebo and metformin and a sulfonylurea.

Combination Therapy: Add-on with Insulin (with or without metformin)

In a 24-week placebo-controlled study of sitagliptin 100 mg in combination with stable dose insulin (with or without metformin) (sitagliptin, N=322; placebo, N=319), the incidence of adverse reactions, reported regardless of causality assessment, in ≥1% of patients are shown in Table 7. The overall incidence of adverse events with sitagliptin was higher than with placebo, in part related to higher incidence of hypoglycemia (see Table 7).

Table 7 – Adverse Events ≥1% in Any Treatment Group (regardless of causality) Reported in Patients in a 24-Week Placebo-Controlled, Double-Blind Clinical Trial of sitagliptin in Add-on Combination Use with Stable Dose Insulin (With or Without Metformin)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Insulin (+/- Metformin) n=322**	**Placebo + Insulin (+/- Metformin) n=319**
Gastrointestinal Disorders		
Constipation	6 (1.9)	1 (0.3)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Insulin (+/- Metformin) n=322**	**Placebo + Insulin (+/- Metformin) n=319**
Diarrhea	6 (1.9)	5 (1.6)
Nausea	4 (1.2)	5 (1.6)
Vomiting	5 (1.6)	2 (0.6)
Infections and infestations		
Bronchitis	6 (1.9)	5 (1.6)
Gastroenteritis	3 (0.9)	5 (1.6)
Influenza	13 (4.0)	12 (3.8)
Nasopharyngitis	10 (3.1)	8 (2.5)
Sinusitis	4 (1.2)	4 (1.3)
Upper respiratory tract infection	10 (3.1)	11 (3.4)
Urinary tract infection	9 (2.8)	6 (1.9)
Investigations		
Alanine aminotransferase increased	4 (1.2)	1 (0.3)
Creatinine renal clearance decreased	5 (1.6)	0 (0.0)
Metabolism and nutrition disorders		
Hyperglycemia	5 (1.6)	2 (0.6)
Hypoglycemia	50 (15.5)	25 (7.8)
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (1.2)	6 (1.9)
Back pain	6 (1.9)	2 (0.6)
Muscle spasms	3 (0.9)	5 (1.6)
Pain in extremity	6 (1.9)	3 (0.9)
Nervous system disorders		
Dizziness	5 (1.6)	3 (0.9)
Headache	9 (2.8)	3 (0.9)
Respiratory, thoracic and mediastinal disorders		
Cough	5 (1.6)	3 (0.9)

In a combination therapy study with stable dose insulin (with or without metformin), hypoglycemia (sitagliptin 9.6%; placebo 5.3%), influenza (sitagliptin 1.2%; placebo 0.3%), and headache (sitagliptin 1.2%; placebo 0.0%) were the only drug-related adverse reactions reported by the investigator that occurred with an incidence ≥1% in patients receiving sitagliptin and greater than in patients receiving placebo.

Combination Therapy: Sitagliptin Add-on to Pioglitazone (with or without Metformin)

In a 24-week placebo-controlled clinical study of patients receiving sitagliptin (100 mg daily) as add-on combination therapy with pioglitazone, the incidence of adverse events reported regardless of causality assessment, in ≥1% of patients are shown in Table 8.

Table 8 – Adverse Events ≥1% in Any Treatment Group (regardless of causality) Reported in Patients in a 24-Week Placebo-Controlled, Double-Blind Clinical Trial of sitagliptin in Add-on Combination with Pioglitazone

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Pioglitazone n=175**	**Placebo + Pioglitazone n=178**
Ear and Labyrinth Disorders		
Vertigo	0 (0.0)	3 (1.7)
Eye Disorders		
Cataract	0 (0.0)	3 (1.7)
Vision Blurred	2 (1.1)	1 (0.6)
Gastrointestinal disorders		
Abdominal pain	2 (1.1)	0 (0.0)
Abdominal pain lower	2 (1.1)	0 (0.0)
Abdominal pain upper	2 (1.1)	0 (0.0)
Constipation	2 (1.1)	2 (1.1)
Diarrhea	3 (1.7)	2 (1.1)
Dyspepsia	2 (1.1)	1 (0.6)
Flatulence	2 (1.1)	0 (0.0)
Nausea	2 (1.1)	0 (0.0)
General disorders and administration site conditions		
Chest pain	2 (1.1)	0 (0.0)
Fatigue	1 (0.6)	3 (1.7)
Feeling abnormal	2 (1.1)	0 (0.0)
Oedema	2 (1.1)	1 (0.6)
Oedema peripheral	7 (4.0)	5 (2.8)
Hepatobiliary Disorders		
Cholelithiasis	0 (0.0)	2 (1.1)
Infections and infestations		
Bronchitis	3 (1.7)	1 (0.6)
Cellulitis	2 (1.1)	1 (0.6)
Influenza	6 (3.4)	5 (2.8)
Nasopharyngitis	7 (4.0)	7 (3.9)
Pharyngitis	2 (1.1)	2 (1.1)
Pneumonia	0 (0.0)	3 (1.7)
Pyoderma	2 (1.1)	0 (0.0)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Pioglitazone n=175**	**Placebo + Pioglitazone n=178**
Sinusitis	2 (1.1)	2 (1.1)
Tinea Pedis	2 (1.1)	0 (0.0)
Upper respiratory tract infection	11 (6.3)	6 (3.4)
Urinary tract infection	1 (0.6)	2 (1.1)
Viral infection	2 (1.1)	1 (0.6)
Injury, poisoning and procedural complications		
Joint sprain	2 (1.1)	2 (1.1)
Investigations		
Blood glucose increased	1 (0.6)	2 (1.1)
Weight increased	5 (2.9)	5 (2.8)
Metabolism and nutrition disorders		
Hypoglycemia	2 (1.1)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	5 (2.9)	4 (2.2)
Back pain	3 (1.7)	5 (2.8)
Musculoskeletal stiffness	2 (1.1)	0 (0.0)
Myalgia	0 (0.0)	2 (1.1)
Neck pain	0 (0.0)	2 (1.1)
Osteoarthritis	3 (1.7)	3 (1.7)
Pain in extremity	4 (2.3)	3 (1.7)
Tendonitis	0 (0.0)	2 (1.1)
Nervous system disorders		
Dizziness	3 (1.7)	2 (1.1)
Headache	9 (5.1)	7 (3.9)
Psychiatric disorders		
Anxiety	1 (0.6)	2 (1.1)
Depression	4 (2.3)	2 (1.1)
Libido decreased	2 (1.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
Cough	3 (1.7)	3 (1.7)
Skin and subcutaneous tissue disorders		
Dermatitis allergic	0 (0.0)	2 (1.1)

In a combination therapy study with pioglitazone, hypoglycemia (sitagliptin 1.1%; placebo 0.0%), flatulence (sitagliptin 1.1%; placebo 0.0%), weight increase (sitagliptin 2.3%; placebo 1.7%), and

headache (sitagliptin 1.7%; placebo 1.1%) were the only drug-related adverse reactions reported by the investigator that occurred with an incidence ≥1% in patients receiving sitagliptin and greater than in patients receiving placebo.

In a 26-week placebo-controlled clinical study of patients receiving sitagliptin (100 mg daily) as add-on combination therapy with metformin and pioglitazone, the incidence of adverse events reported regardless of causality assessment, in ≥1% of patients are shown in Table 9.

Table 9 – Adverse Events ≥1% in Any Treatment Group (regardless of causality) Reported in Patients in a 26-Week Placebo-Controlled, Double-Blind Clinical Trial of sitagliptin in Add-on Combination Use with Metformin and Pioglitazone

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Pioglitazone n=157**	**Placebo + Metformin + Pioglitazone n=156**
Ear and Labyrinth Disorders		
Cerumen impaction	2 (1.3)	1 (0.6)
Eye Disorders		
Conjunctivitis	3 (1.9)	1 (0.6)
Ocular hyperaemia	0 (0.0)	2 (1.3)
Gastrointestinal disorders		
Abdominal pain upper	1 (0.6)	2 (1.3)
Constipation	2 (1.3)	1 (0.6)
Dental Caries	2 (1.3)	1 (0.6)
Diarrhea	3 (1.9)	4 (2.6)
Dyspepsia	1 (0.6)	2 (1.3)
Gastritis	0 (0.0)	2 (1.3)
Toothache	2 (1.3)	0 (0.0)
Vomiting	2 (1.3)	0 (0.0)
General disorders and administration site conditions		
Fatigue	0 (0.0)	2 (1.3)
Oedema peripheral	3 (1.9)	7 (4.5)
Infections and infestations		
Bronchitis	3 (1.9)	1 (0.6)
Cellulitis	2 (1.3)	0 (0.0)
Gastroenteritis	2 (1.3)	0 (0.0)
Gastroenteritis viral	2 (1.3)	0 (0.0)
Herpes zoster	2 (1.3)	0 (0.0)
Influenza	2 (1.3)	3 (1.9)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Pioglitazone n=157**	**Placebo + Metformin + Pioglitazone n=156**
Nasopharyngitis	5 (3.2)	5 (3.2)
Tooth abscess	0 (0.0)	2 (1.3)
Upper respiratory tract infection	13 (8.3)	14 (9.0)
Urinary tract infection	5 (3.2)	6 (3.8)
Injury, poisoning and procedural complications		
Muscle strain	2 (1.3)	0 (0.0)
Investigations		
Blood creatine phosphokinase increased	1 (0.6)	3 (1.9)
Glomerular filtration rate decreased	2 (1.3)	0 (0.0)
Lymphocyte count increased	2 (1.3)	1 (0.6)
Neutrophil count decreased	2 (1.3)	1 (0.6)
Metabolism and nutrition disorders		
Hyperglycemia	2 (1.3)	2 (1.3)
Hypoglycemia	10 (6.4)	7 (4.5)
Musculoskeletal and connective tissue disorders		
Arthralgia	2 (1.3)	3 (1.9)
Back pain	7 (4.5)	4 (2.6)
Muscle spasms	2 (1.3)	0 (0.0)
Musculoskeletal pain	3 (1.9)	4 (2.6)
Pain in extremity	5 (3.2)	2 (1.3)
Nervous system disorders		
Headache	1 (0.6)	2 (1.3)
Psychiatric disorders		
Depression	4 (2.5)	1 (0.6)
Stress	2 (1.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
Cough	2 (1.3)	2 (1.3)
Oropharyngeal pain	2 (1.3)	0 (0.0)
Rhinitis allergic	2 (1.3)	0 (0.0)

In a combination therapy study with pioglitazone and metformin, hypoglycemia (Sitagliptin 3.2%; placebo 1.9%) was the only drug-related adverse reaction reported by the investigator that occurred with an incidence ≥1% in patients receiving sitagliptin and greater than in patients

receiving placebo.

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Drug Reactions ≥0.1% and <1% (Drug-Related and Greater than Placebo in Pooled Monotherapy and in Individual Placebo-Controlled Studies)

Blood and Lymphatic System Disorders: anemia
Cardiac Disorders: bundle branch block, palpitations **Eye Disorders:** vision blurred
Gastrointestinal Disorders: abdominal discomfort, abdominal pain upper, abdominal tenderness, constipation, diarrhea, dry mouth, dyspepsia, flatulence, reflux esophagitis disease, frequent bowel movements, gastroesophageal reflux disease, irritable bowel syndrome, retching, salivary hypersecretion **General Disorders and Administration Site Conditions:** asthenia, chest discomfort, face edema, fatigue, feeling abnormal, hunger, irritability, malaise, peripheral edema, edema, pain, pyrexia, thirst, xerosis **Hepatobiliary Disorders:** hepatic steatosis
Infections and Infestations: gastric ulcer helicobacter, genital abscess, helicobacter gastritis, localized infection, oropharyngeal candidiasis, sinusitis, upper respiratory tract infection, urinary tract infection **Investigations:** alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose decreased, blood glucose increased, blood pressure decreased, blood pressure increased, creatinine renal clearance decreased, glomerular filtration rate decreased, white blood cell count increased
Metabolism and Nutrition Disorders: decreased appetite, hypoglycemia
Musculoskeletal and Connective Tissue Disorders: muscle fatigue, muscle tightness
Nervous System Disorders: coordination abnormal, dizziness, headache, migraine, neuropathy peripheral, parosmia, somnolence
Psychiatric Disorders: anxiety, depression, insomnia, libido decreased
Renal and Urinary Disorders: renal disorders
Reproductive System and Breast Disorders: balanoposthitis, dysmenorrhea, erectile dysfunction
Respiratory, Thoracic and Mediastinal Disorders: cough
Skin and Subcutaneous Tissue Disorders: angioneurotic oedema, dermatitis acneiform, dry skin, erythema, exanthem, hyperhidrosis, leukocytoclastic vasculitis, nail disorder, prurigo, pruritus generalized, rash, rash macular, rosacea, urticaria
Vascular Disorders: orthostatic hypotension

Atrial fibrillation/atrial flutter: In a pooled analysis of randomized clinical trials, the pooled terms atrial fibrillation/atrial flutter were observed at an incidence rate of 0.45 events per 100 patient-years in the sitagliptin-exposed group compared to 0.28 events per 100 patient-years in the non-exposed group.

TECOS Cardiovascular Safety Study:
For details pertaining to study design and patient population, see 14 CLINICAL TRIALS, TECOS Cardiovascular Safety Study.

The incidence of adjudication-confirmed pancreatitis events was higher in the sitagliptin group (0.3%) compared to the placebo group (0.2%). The sitagliptin group experienced a greater number of severe cases of pancreatitis including two confirmed deaths due to pancreatitis, compared to

none in the placebo group.

Among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 2.7% in patients treated with sitagliptin and 2.5% in patients treated with placebo; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 1.0% in patients treated with sitagliptin and 0.7% in placebo-treated patients.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin 100 mg compared to patients treated with placebo. In most clinical studies, a slight decrease in alkaline phosphatase and small increases in uric acid and white blood cell (WBC) count (due to an increase in neutrophils) were observed. In active comparator studies versus metformin or versus a sulfonylurea agent (glipizide) similar changes were seen in alkaline phosphatase and uric acid.

Mean Change from Baseline (Standard Error)				
Study	**Treatment Group**	**Alkaline Phosphatase (IU/L)**	**Uric Acid (mg/dL)**	**WBC (cell/microl)**
Placebo-controlled (monotherapy)[1]	Sitagliptin	-5.3 (0.5)	0.26 (0.04)	320.2 (71.7)
	Placebo	-0.8 (0.5)	-0.05 (0.05)	58.6 (80.0)
Active-controlled (monotherapy)[2]	Sitagliptin	-3.9 (0.5)	-0.0 (0.0)	220.4 (77.7)
	Metformin	-4.7 (0.5)	0.1 (0.0)	184.7 (66.6)
Placebo-controlled (add-on to metformin)[3]	Sitagliptin	-3.1 (0.4)	0.17 (0.04)	346.0 (64.3)
	Placebo	-1.3 (0.7)	0.05 (0.06)	142.4 (98.8)
Active-controlled (add-on to metformin)[4]	Sitagliptin	-5.7 (0.5)	0.21 (0.05)	207.8 (67.4)
	Glipizide	-3.4 (0.5)	0.20 (0.05)	86.0 (62.5)

1 pooled data from studies 3 and 4; see 14 CLINICAL TRIALS, Table 11

2 study 5; see 14 CLINICAL TRIALS, Table 11

3 study 1; see 14 CLINICAL TRIALS, Table 11

4 study 2; see 14 CLINICAL TRIALS, Table 11

In a combination therapy study with stable dose insulin (with or without metformin), a greater proportion of patients was observed to have a decrease in hemoglobin ≥1.5 g/dL in the sitagliptin group (6.0%) compared with the placebo group (2.1%). No adverse experiences of anemia or hemoglobin decreased were reported in the sitagliptin group.

8.5 Post-Market Adverse Reactions

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.

Gastrointestinal disorders: acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see 7 WARNINGS AND PRECAUTIONS); vomiting
Immune system disorders: hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions, including Stevens-Johnson syndrome (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS)
Musculoskeletal and connective tissue disorders: arthralgia, myalgia, pain in extremity, back pain, rhabdomyolysis
Renal and urinary disorders: worsening renal function, including acute renal failure (sometimes requiring dialysis) (see 7 WARNINGS AND PRECAUTIONS)
Skin and subcutaneous tissue disorders: pruritus, bullous pemphigoid (see 7 WARNINGS AND PRECAUTIONS)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

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

9.3 Drug-Behavioural Interactions

Effects of Smoking, Alcohol, and Diet: The effects of smoking, diet, and alcohol use on the pharmacokinetics of sitagliptin have not been specifically studied.

9.4 Drug-Drug Interactions

In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Multiple doses of sitagliptin slightly increased digoxin concentrations; however, these increases are not considered likely to be clinically meaningful and are not attributed to a specific mechanism.

Effects of other drugs on the pharmacokinetics of sitagliptin
Metformin: Co-administration of multiple twice-daily doses of metformin with sitagliptin did not

meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

Cyclosporine: A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of cyclosporine increased the area under the plasma concentration versus time curve (AUC) and C_{max} of sitagliptin by approximately 29% and 68%, respectively. These modest changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Effects of sitagliptin on the pharmacokinetics of other drugs
Metformin: Co-administration of multiple twice-daily doses of sitagliptin with metformin, an OCT substrate, did not meaningfully alter the pharmacokinetics of metformin or sitagliptin in patients with type 2 diabetes. Therefore, sitagliptin is not an inhibitor of OCT-mediated transport.

Sulfonylureas: Single-dose pharmacokinetics of glyburide, a CYP2C9 substrate, were not meaningfully altered in subjects receiving multiple doses of sitagliptin. Clinically meaningful interactions would not be expected with other sulfonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glyburide, are primarily eliminated by CYP2C9.

Simvastatin: Single-dose pharmacokinetics of simvastatin, a CYP3A4 substrate, were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP3A4-mediated metabolism.

Thiazolidinediones: Single-dose pharmacokinetics of rosiglitazone were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP2C8- mediated metabolism. Clinically meaningful interactions with pioglitazone are not expected because pioglitazone predominantly undergoes CYP2C8- or CYP3A4-mediated metabolism.

Warfarin: Multiple daily doses of sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin International Normalized Ratio) of a single-dose of warfarin. Since S(-) warfarin is primarily metabolized by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.

Oral Contraceptives: Co-administration with sitagliptin did not meaningfully alter the steady state pharmacokinetics of norethindrone or ethinyl estradiol.

Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma C_{max} by 18%. These increases are not considered likely to be clinically meaningful. No dosage adjustment of digoxin or PRZ-SITAGLIPTIN is recommended.

9.5 Drug-Food Interactions

There are no known interactions with food.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Sitagliptin is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a novel class of agents that act as incretin enhancers.

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. 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. Progressive beta-cell failure is a feature characterizing the pathogenesis of type 2 diabetes. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced.

In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. When blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. GLP-1 does not impair the normal glucagon response to hypoglycemia.

The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP- 4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner.

In patients with type 2 diabetes with hyperglycemia, these changes in insulin and glucagon levels lead to lower hemoglobin A_{1c} (HbA_{1c}) and lower fasting and postprandial glucose concentrations. Sitagliptin demonstrates selectivity for DPP-4, and does not inhibit the DPP-8 or DPP-9 activity *in vitro* at concentrations approximating those from therapeutic doses. Inhibition of DPP-8 or DPP-9, but not DPP-4, is associated with toxicity in preclinical animal models and alteration of immune function *in vitro.*

Sitagliptin was assessed for its ability to improve glucose tolerance in lean and diet-induced obese (DIO) mice following dextrose challenge and in diabetic (db/db) mice. In lean and DIO mice, single oral doses of sitagliptin reduced blood glucose levels in a dosage-dependent manner. Acute lowering of blood glucose was also demonstrated in diabetic db/db mice. A 2- to 3-fold increase in active GLP-1 was seen at the maximally effective dose of 1 mg/kg sitagliptin in lean mice. These results are consistent with the action of sitagliptin as an anti-hyperglycemic agent.

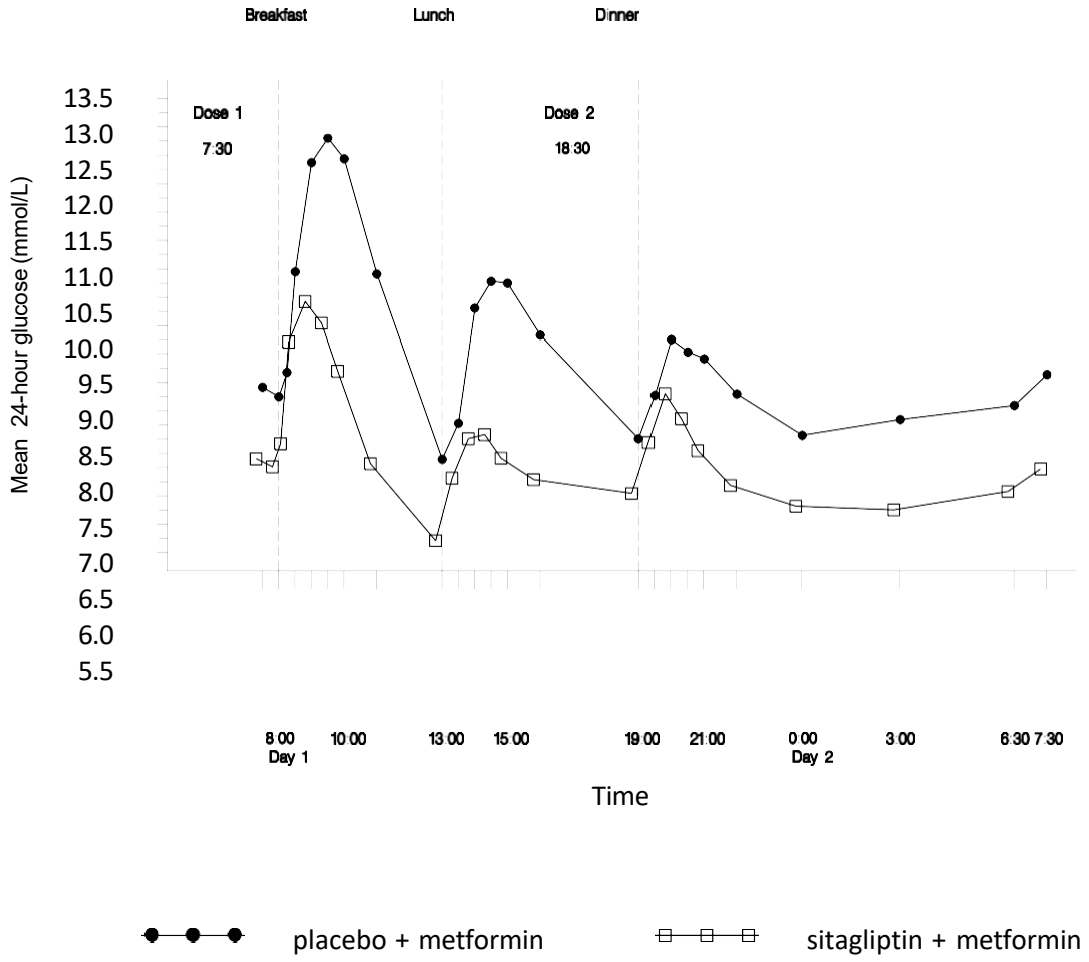
Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose, stimulate insulin biosynthesis and release, increase beta cell neogenesis, and decrease beta cell death. The effects on beta cell neogenesis and beta cell death have not been studied in humans.

10.2 Pharmacodynamics

In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24-hour period, resulting in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose excursion following an oral glucose load or a meal.

In a study of patients with type 2 diabetes inadequately controlled on metformin monotherapy (N=26), glucose levels monitored throughout the day were significantly lower ($p<0.001$) in patients who received sitagliptin 100 mg per day (50 mg twice daily) in combination with metformin compared with patients who received placebo with metformin (see Figure 1).

Figure 1 – 24-Hour Plasma Glucose Profile After 4-Week Treatment with Sitagliptin 50 mg BID with Metformin or Placebo with Metformin



In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia, suggesting that the insulinotropic and glucagon suppressive actions of the drug are glucose dependent.

Cardiac Electrophysiology: In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline at 3 hours post- dose was 8.0 msec (90% CI; 5.5, 10.6). At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100 mg dose.

In patients with type 2 diabetes administered sitagliptin 100 mg (N=81) or sitagliptin 200 mg

(N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

10.3 Pharmacokinetics

Table 10 – Summary of Sitagliptin's Pharmacokinetic Parameters in Healthy Volunteers

	Cmax nM	t½ (h)	AUC0-∞ mcM•hr	Renal Clearance mL/min	Volume of distribution (L)*
Single oral dose (100 mg) mean	950	12.4	8.52	350	198

* Volume of distribution at steady state following an I.V. dose.

The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes. 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 post-dose.
Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100 mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 mcM•hr, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin 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 were generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption: The absolute bioavailability of sitagliptin is approximately 87%. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Distribution: 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%).

Metabolism: Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine.

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.

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

sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

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

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in pediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18% lower compared to adult patients with type 2 diabetes for a 100 mg dose.

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

  Health Canada has not authorized an indication for pediatric use.

- **Geriatrics:** Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

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

- **Ethnic Origin:** Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data, including subjects of White, Hispanic, Black and Asian racial groups.

- **Hepatic Insufficiency:** In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% (90% CI: 1%, 46%) and 13% (90% CI: -9%, 42%), respectively, compared to healthy matched controls following administration of a single 100 mg dose of sitagliptin.

- **Renal Insufficiency:** A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50 mg) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment as well as patients with ESRD on hemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses.

Compared to normal healthy control subjects, an approximate 1.2 to 1.6-fold increase in plasma AUC of sitagliptin was observed in patients with mild renal impairment (eGFR ≥60 mL/min/1.73 m^2 to <90 mL/min/1.73 m^2) and patients with moderate renal impairment (eGFR ≥45 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2), respectively, which is not a clinically meaningful increase to require dosage adjustment.

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

To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with an eGFR <45 mL/min/1.73 m^2 including patients with severe renal impairment and patients with ESRD on hemodialysis (see 7 WARNINGS AND PRECAUTIONS, 4 DOSAGE AND ADMINISTRATION and 14 CLINICAL TRIALS).

11 STORAGE, STABILITY AND DISPOSAL

Preserve in well-closed containers. Store at room temperature (15°C to 30°C).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

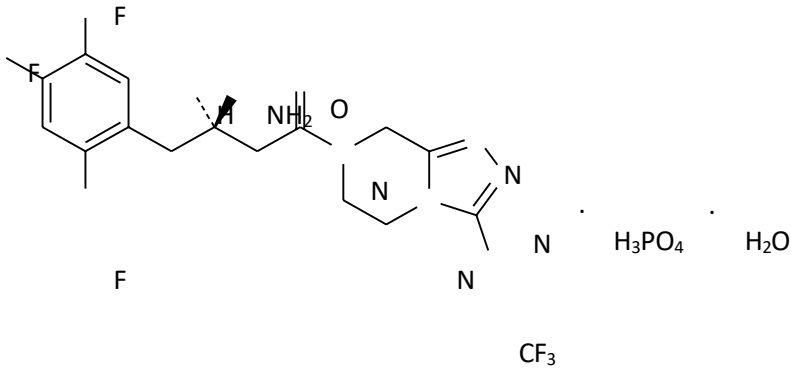
Proper name: Sitagliptin Phosphate Monohydrate

Chemical name: (3R)-3-Amino-l-[3-(trifluoromethyl)-5,6-dihydro [1,2,4] triazolo [4,3-a] pyrazin-7(8H)-yl]-4-(2,4,5 trifluoro phenyl) butan-1-one phosphate monohydrate.

Molecular formula: $C_{16}H_{18}F_6N_5O_5P,H2O$

Molecular mass: 523.3 g/mol

Structural formula:



Physicochemical properties: Sitagliptin phosphate monohydrate is a white or almost white powder, crystalline, non-hygroscopic powder. It is soluble in water very slightly soluble in anhydrous ethanol, practically insoluble in heptane.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Monotherapy

Placebo-Controlled Study

Table 11 – Summary of Study Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P023	Multicentre, randomized, double-blind, placebo-controlled	Placebo or 100 mg or 200 mg Sitagliptin once daily Oral 18-week	521	55.1 years (27–76)	Male: 283 Female: 238
P021	Multicentre, randomized, double-blind, placebo-controlled	Placebo or 100 mg or 200 mg Sitagliptin once daily Oral 24-week	741	54.2 years (18–75)	Male: 383 Female: 358

A total of 1262 patients with type 2 diabetes participated in two double-blind, placebo-controlled studies, one of 18-week and another of 24-week duration, to evaluate the efficacy and safety of sitagliptin monotherapy. Patients with inadequate glycemic control (HbA_{1c} 7% to 10%) were randomized to receive a 100 mg or 200 mg dose of sitagliptin or placebo once daily.

Treatment with sitagliptin at 100 mg daily provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo (Table 12). The improvement in HbA_{1c} compared to placebo was not affected by gender, age, race, prior antihyperglycemic therapy or baseline BMI. Patients with a shorter length of time since diagnosis of diabetes (<3 years) or with higher baseline HbA_{1c} had greater reductions in HbA_{1c}. 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 the baseline with sitagliptin (mean weight loss of 0.6 kg in the 18-week study and 0.2 kg in the 24-week study). Patients on placebo lost more weight (mean weight loss 0.7 kg in the 18-week study and 1.1 kg in the 24-week study) than patients on sitagliptin.

Table 12 – Glycemic Parameters in 18-and 24-Week Placebo-Controlled Studies of sitagliptin in Patients with Type 2 Diabetes[†]

	18-Week Study		24-Week Study	
	Sitagliptin 100 mg	**Placebo**	**Sitagliptin 100 mg**	**Placebo**
HbA_{1c} (%)	**N=193**	**N=103**	**N=229**	**N=244**
Baseline (mean)	8.0	8.1	8.0	8.0
Change from Baseline (adjusted mean[‡])	-0.5	0.1	-0.6	0.2
Difference from Placebo(adjusted mean[‡])	-0.6[§]		-0.8[§]	
Patients (%) achieving HbA_{1c} <7%	69[§] (35.8%)	16 (15.5%)	93[§] (40.6%)	41 (16.8%)
FPG (mmol/L)	**N=201**	**N=107**	**N=234**	**N=247**
Baseline (mean)	10.0	10.2	9.5	9.8
Change from baseline (adjusted mean[‡])	-0.7	0.4	-0.7	0.3
Difference from Placebo(adjusted mean[‡])	-1.1[§]		-1.0[§]	
2-hour PPG (mmol/L)	**NA**	**NA**	**N=201**	**N=204**
Baseline (mean)			14.3	15.0
Change from baseline (adjusted mean[‡])			-2.7	-0.1
Difference from Placebo (adjusted mean[‡])			-2.6[§]	

[†] All Patients Treated Population (an intention-to-treat analysis).

[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

[§] p<0.001 compared to placebo.

[NA] Data not available.

Active-Controlled Study with Metformin

Table 13 – Summary of Study Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P049	Multicentre, randomized double-blind active-controlled	Sitagliptin 100 mg/ day or Metformin 500 mg/ day and titrated to 1500 to 2000 mg/day Oral 24 Weeks	1050	56.0 years (20–78)	Male: 484 Female: 566

The efficacy of sitagliptin compared to that of metformin was evaluated in a 24-week, double-

blind, metformin-controlled trial in patients with type 2 diabetes and inadequate glycemic control on diet and exercise and who were not on antihyperglycemic therapy (off therapy for at least 4 months). In this study, patients with an HbA_{1c} of 6.5% to 9.0% were randomized to receive either sitagliptin 100 mg daily (N=528) or metformin (N=522) for 24 weeks. Patients receiving metformin were given an initial dosage of 500 mg/day and then titrated to a dose of 1500 to 2000 mg/day over a period of up to 5 weeks based on tolerability. The mean dose of metformin after the titration period was approximately 1900 mg/day. Glycemic endpoints measured included HbA_{1c} and fasting glucose.

Both treatments resulted in a statistically significant improvement in glycemic control from baseline. At 24 weeks, the reduction from baseline in HbA_{1c} was -0.43% for sitagliptin 100 mg daily and -0.57% for metformin in the per protocol population analysis.

The reduction in FPG was -0.64 mmol/L for sitagliptin and -1.08 mmol/L for metformin. Body weight decreased from baseline in both treatment groups (sitagliptin:-0.6 kg; metformin: -1.9 kg).

Sitagliptin in Combination with Metformin

Placebo-Controlled Study

Table 14 – Summary of Study Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P020	Multicentre, randomized, double-blind, placebo-controlled	Sitagliptin 100 mg once daily+ ≥1500 mg/day Metformin or Placebo + ≥1500 mg/day Metformin Oral 24-week	701	54.5 years (19–78)	Male: 400 Female: 301

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin. All patients were started on metformin monotherapy and the dose increased to at least 1500 mg per day. Patients were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients with congestive heart failure requiring pharmacological treatment were excluded from this study.

Glycemic parameters and body weight at final visit (24-week study) for sitagliptin in combination with metformin are shown in Table 15.

Table 15 – Glycemic Parameters and Body Weight at Final Visit (24-week study) for sitagliptin in Combination with Metformin†

	Sitagliptin 100 mg+ Metformin	Placebo + Metformin
HbA_{1c} (%)	**N=453**	**N=224**
Baseline (mean)	8.0	8.0
Change from baseline (adjusted mean‡)	-0.7	-0.0
Difference from placebo + metformin (adjusted mean‡)	-0.7§	
Patients (%) achieving HbA_{1c} <7%	213 (47.0%)	41 (18.3%)
FPG (mmol/L)	**N=454**	**N=226**
Baseline (mean)	9.4	9.6
Change from baseline (adjusted mean‡)	-0.9	0.5
Difference from placebo + metformin (adjusted mean‡)	-1.4§	
2-hour PPG (mmol/L)	**N=387**	**N=182**
Baseline (mean)	15.3	15.1
Change from baseline (adjusted mean‡)	-3.4	-0.6
Difference from placebo + metformin (adjusted mean‡)	-2.8§	
Body Weight (kg)*	**N=399**	**N=169**
Baseline (mean)	86.9	87.6
Change from baseline (adjusted mean‡)	-0.7	-0.6
Difference from placebo + metformin (adjusted mean‡)	-0.1¶	

† All Patients Treated Population (an intention-to-treat analysis).

‡ Least squares means adjusted for prior antihyperglycemic therapy and baseline value.

§ p<0.001 compared to placebo + metformin.

* All Patients as Treated (APaT) population, excluding patients given glycemic rescue therapy.

¶ Not statistically significant (p□0.05) compared to placebo + metformin.

Active-Controlled (Sulfonylurea Agent) Study

Table 16 – Summary of Study Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P024	Multicentre, randomized, double- blind, with an active comparator	Sitagliptin 100 mg/ day + ≥1500 mg/day Metformin or Glipizide 5–20 mg/ day + ≥1500 mg/day Metformin Oral 52-week	1172	Male 23–79 Female 22–78	Male: 694 Female: 478

Long-term maintenance of effect was evaluated in a 52-week, double-blind, glipizide-controlled trial in patients with type 2 diabetes and inadequate glycemic control on metformin monotherapy at ≥1500 mg/day. In this study, patients were randomized to the addition of either sitagliptin 100 mg daily (N=588) or glipizide (N=584) for 52 weeks. Patients receiving glipizide were given an initial dosage of 5 mg/day and then electively titrated by the investigator to a target FPG of 6.1 mmol/L, without significant hypoglycemia, over the next 18 weeks. A maximum dosage of 20 mg/day was allowed to optimize glycemic control. Thereafter, the glipizide dose was to have been kept constant. The mean daily dose of glipizide after the titration period was 10.3 mg.

Both treatments resulted in a statistically significant improvement in glycemic control from baseline. After 52 weeks, the reduction from baseline in HbA_{1c} was 0.67% for sitagliptin 100 mg daily and 0.67% for glipizide, confirming the non-inferiority of sitagliptin compared to glipizide. The reduction in FPG was 0.6 mmol/L for sitagliptin and 0.4 mmol/L for glipizide. In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with sitagliptin relative to glipizide. The incidence of hypoglycemia in the sitagliptin group (4.9%) was significantly lower than that in the glipizide group (32.0%). Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs. +1.1 kg).

Sitagliptin Add-on Combination Therapy

Add-on Combination Therapy with Metformin plus Glimepiride

Table 17 – Summary of Study Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P035	Multicentre, randomized, double-blind, placebo-controlled	Sitagliptin 100 mg/day + Glimepiride ≥4 mg/day in Combination with Metformin ≥1500 mg/day or Placebo + Glimepiride ≥4 mg/day in combination with Metformin ≥1500 mg/day Oral 24-week	229	58.0 years (33–75)	Male: 120 Female: 109

In a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin 100 mg once daily (N=116) compared to placebo (N=113), 229 patients were on the combination of glimepiride (≥4 mg per day) and metformin (≥1500 mg per day); the results of the glycemic endpoints, including HbA_{1c} and FPG, are described below.

The combination of sitagliptin, glimepiride, and metformin provided significant reduction from baseline in HbA_{1c} and FPG compared to placebo (see Table 18). Mean reductions from baseline in HbA_{1c} compared with placebo were generally greater for patients with higher baseline HbA_{1c} values. Patients treated with sitagliptin, had a modest increase in body weight (0.4 kg) compared to those given placebo who had a significant decrease in body weight (-0.7 kg).

Table 18 – Glycemic Parameters and Body Weight at Final Visit (24-Week Study) for sitagliptin in Add-on Combination Therapy with Metformin plus Glimepiride[†]

	Sitagliptin 100 mg + Metformin + Glimepiride	Placebo + Metformin + Glimepiride
HbA1c (%)	**N=115**	**N=105**
Baseline (mean)	8.27	8.28
Change from baseline (adjusted mean[‡])	-0.59	0.30
Difference from placebo (adjusted mean[‡])	-0.89[§]	
Patients (%) achieving HbA1c <7%	26 (22.6)	1 (1.0)
FPG (mmol/L)	**N=115**	**N=109**
Baseline (mean)	9.95	9.93
Change from baseline (adjusted mean[‡])	-0.43	0.72
Difference from placebo (adjusted mean[‡])	-1.15[§]	
Body Weight (kg)[*]	**N=102**	**N=74**
Baseline (mean)	86.5	84.6
Change from baseline (adjusted mean[‡])	0.4	-0.7
Difference from placebo (adjusted mean[‡])	1.1[††]	

[†] All Patients Treated Population (an intention-to-treat analysis).

[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

[§] p<0.001 compared to placebo.

* All Patients as Treated (APaT) population, excluding patients given glycemic rescue therapy.

[††] p=0.007 compared to placebo.

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

Table 19 – Summary of Study Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P051	Multicentre, randomized, double- blind placebo- controlled	Sitagliptin 100 mg/day + Stable dose insulin (alone or in combination with metformin ≥1500 mg/day) or Placebo + stable dose insulin (alone or in combination with metformin ≥1500 mg/day)	641	57.8 years (25–82)	Male: 326 Female: 315

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
		24-week			

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin as add-on combination therapy with a stable dose of insulin (with or without metformin). Patients with an HbA_{1c} of 7.5% to 11.0% while on a stable regimen of pre-mixed, long-acting, or intermediate-acting insulin with or without metformin (≥1500 mg per day) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients using pre-meal short-acting or rapid-acting insulins that were not components of a pre-mixed insulin formulation, or that were administered via insulin pumps, were not included in this study. Glycemic endpoints measured included HbA_{1c}, fasting glucose, and 2-hour post- prandial glucose.

In combination with insulin (including patients taking and not taking metformin), sitagliptin provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo (Table 20). There was no significant difference between sitagliptin and placebo in body weight change.

Table 20 – Glycemic Parameters and Body Weight at Final Visit (24-Week Study) for Sitagliptin as Add-on Combination Therapy with a Stable Dose of Insulin (with or without Metformin[†])

	Sitagliptin 100 mg + Insulin (+/- Metformin)	Placebo + Insulin (+/- Metformin)
HbA_{1c} (%)	**N=305**	**N=312**
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean[‡])	-0.6	-0.0
Difference from placebo (adjusted mean[‡,§])	-0.6[*]	
Patients (%) achieving HbA_{1c} <7%	39 (12.8)	16 (5.1)
FPG (mmol/L)	**N=310**	**N=313**
Baseline (mean)	9.7	9.8
Change from baseline (adjusted mean[‡])	-1.0	-0.2

	Sitagliptin 100 mg + Insulin (+/- Metformin)	Placebo + Insulin (+/- Metformin)
Difference from placebo (adjusted mean‡)	-0.8	
2-hour PPG (mmol/L)	**N=240**	**N=257**
Baseline (mean)	16.0	16.1
Change from baseline (adjusted mean‡)	-1.7	0.3
Difference from placebo (adjusted mean‡)	-2.0*	
Body Weight (kg)¶	**N=266**	**N=266**
Baseline (mean)	86.6	87.4
Change from baseline (adjusted mean‡)	0.1	0.1
Difference from placebo (adjusted mean‡)	0.0#	

† All Patients Treated Population (an intention-to-treat analysis).

‡ Least squares means adjusted for metformin use at Visit 1 (yes/no), insulin use at Visit 1 (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.

¶ All Patients as Treated (APaT) population, excluding data following glycemic rescue therapy.

Not statistically significant (p 0.05) compared to placebo.

Table 21 – Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin as Add-on Combination Therapy with a Stable Dose of Insulin (with or without Metformin[†])

	Sitagliptin 100 mg + Insulin	Placebo + Insulin	Sitagliptin 100 mg + Insulin + Metformin	Placebo + Insulin + Metformin
HbA_{1c} (%)	**N=82**	**N=83**	**N=223**	**N=229**
Baseline (mean)	8.7	8.8	8.7	8.6
Change from baseline (adjusted mean[‡])	-0.6	0.1	-0.7	-0.1
Difference from placebo (adjusted mean[‡])	-0.7[*]		-0.5[*]	
Patients (%) achieving HbA_{1c} <7%	7 (8.5)	4 (4.8)	32 (14.3)	12 (5.2)
FPG (mmol/L)	**N=85**	**N=84**	**N=225**	**N=229**
Baseline (mean)	10.1	10.5	9.6	9.8
Change from baseline (adjusted mean[‡])	-0.7	-0.3	-1.2	-0.2
Difference from placebo (adjusted mean[‡])	-0.3[§]		-1.0[*]	
2-hour PPG (mmol/L)	**N=58**	**N=68**	**N=182**	**N=189**
Baseline (mean)	17.9	18.0	15.6	15.6
Change from baseline (adjusted mean[‡])	-1.0	0.3	-2.2	0.1
Difference from placebo (adjusted mean[‡])	-1.3[#]		-2.2[*]	

[†] All Patients Treated Population (an intention-to-treat analysis).

[‡] Least squares means adjusted for insulin use at Visit 1 (pre-mixed vs. non-pre-mixed [intermediate- or long- acting]), and baseline value.

* p<0.001 compared to placebo.

[§] Not statistically significant (p□0.05) compared to placebo.

[#] p=0.037 compared to placebo.

Add-on Combination Therapy with Pioglitazone

Table 22 – Summary of Study Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P019	Multicentre, randomized, double-blind, placebo-controlled	Sitagliptin 100 mg/ day + 30 or 45 mg/day Pioglitazone or Placebo + 30 or 45 mg/day Pioglitazone Oral	353	56.2 years (24–87)	Male: 196 Female: 157

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
		24-week			

A total of 353 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with pioglitazone. All patients were on pioglitazone monotherapy at a dose of 30-45 mg per day. Patients were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Glycemic endpoints measured included HbA_{1c} and fasting glucose.

In combination with pioglitazone, sitagliptin provided significant improvements in HbA_{1c} and FPG compared to placebo with pioglitazone (Table 23). The improvement in HbA_{1c} was not affected by baseline HbA_{1c}, prior anti-hyperglycemic therapy, gender, age, race, baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome (according to NCEP criteria), or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA-β). Treatment with sitagliptin did not significantly increase body weight from baseline compared to placebo.

Table 23 – Glycemic Parameters and Body Weight at Final Visit (24-week study) for sitagliptin in Combination with Pioglitazone[†]

	Sitagliptin 100 mg + Pioglitazone	Placebo + Pioglitazone
HbA_{1c} (%)	**N=163**	**N=174**
Baseline (mean)	8.1	8.0
Change from baseline (adjusted mean[‡])	-0.9	-0.2
Difference from pioglitazone alone (adjusted mean[‡])	-0.7[§]	
Patients (%) achieving HbA_{1c} <7%	74 (45.4%)	40 (23.0%)
FPG (mmol/L)	**N=163**	**N=174**
Baseline (mean)	9.3	9.2
Change from baseline (adjusted mean[‡])	-0.9	0.1
Difference from pioglitazone alone (adjusted mean[‡])	-1.0[§]	
Body Weight (kg)[*]	**N=133**	**N=136**
Baseline (mean)	90.0	85.6
Change from baseline (adjusted mean[‡])	1.8	1.5
Difference from pioglitazone alone (adjusted mean[‡])	0.2[¶]	

[†] All Patients Treated Population (an intention-to-treat analysis).

‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

§ p<0.001 compared to placebo + pioglitazone.

*All Patients as Treated (APaT) population, excluding patients given glycemic rescue therapy.

¶ Not statistically significant (p≥0.05) compared to placebo + pioglitazone.

Add-on Combination Therapy with Pioglitazone and Metformin

Table 24 – Summary of Study Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P128	Multicentre, randomized, double-blind, placebo-controlled	Sitagliptin 100 mg/day + Pioglitazone ≥30 mg/day + Metformin ≥1500 mg/day or Placebo + Pioglitazone ≥30 mg/day + Metformin ≥1500 mg/day Oral 26-week	313	56.1 (22–78)	Male: 195 Female: 118

A total of 313 patients with type 2 diabetes participated in a 26-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with pioglitazone and metformin. Patients with inadequate glycemic control on a stable regimen of pioglitazone (30 or 45 mg per day) and metformin (≥1500 mg per day) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily.

In combination with pioglitazone and metformin, sitagliptin provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo with pioglitazone and metformin (Table 25). Lipid effects were generally neutral. The difference between sitagliptin and placebo in body weight change was not significant.

Table 25 – Glycemic Parameters and Body Weight at Final Visit (26-Week Study) for sitagliptin as Add-on Combination Therapy with Pioglitazone and Metformin[†]

	Sitagliptin 100 mg + Pioglitazone 30 or 45 mg + Metformin	Placebo + Pioglitazone 30 or 45 mg + Metformin
HbA_{1c} (%)	**N=152**	**N=153**
Baseline (mean)	8.8	8.6
Change from baseline (adjusted mean[‡])	-1.2	-0.4
Difference from placebo (adjusted mean[‡])	-0.7[§]	
Patients (%) achieving HbA_{1c} <7%	38 (25.0)	15 (9.8)
FPG (mmol/L)	**N=155**	**N=153**
Baseline (mean)	10.0	9.6
Change from baseline (adjusted mean[‡])	-1.1	-0.2
Difference from placebo (adjusted mean[‡])	-1.0[§]	
2-hour PPG (mmol/L)	**N=141**	**N=135**
Baseline (mean)	15.3	14.7
Change from baseline (adjusted mean[‡])	-3.0	-0.8
Difference from placebo (adjusted mean[‡])	-2.2[§]	
Body Weight (kg)[*]	**N=146**	**N=128**
Baseline (mean)	81.4	82.0
Change from baseline (adjusted mean[‡])	1.3	1.1
Difference from placebo (adjusted mean[‡])	0.1[¶]	

[†] Full Analysis Set population (an intention-to-treat analysis).

[‡] Least squares mean adjusted for baseline value.

[§] $p<0.001$ compared to placebo.

* All Patients as Treated (ApaT) population, excluding data following glycemic rescue therapy.

[¶] Not statistically significant ($p\geq0.05$) compared to placebo.

Study in Special Population

Patients with Renal Impairment

Table 26 – Summary of Study Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P063	Multicentre, randomized, double-blind, active-controlled	Sitagliptin 25 or 50 mg/day or Glipizide 2.5 to 20 mg/day Oral 54 weeks	423	64.2 years (33–89)	Male: 253 Female: 170

A study comparing sitagliptin at 25 or 50 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in patients with moderate to severe renal impairment. In this study, 277 patients with chronic renal impairment were included in the Per-protocol population (135 patients on sitagliptin: moderate [n=98], severe [n=37]; and 142 patients on glipizide: moderate [n=106], severe [n=36]).

After 54 weeks, the mean reduction from baseline in HbA_{1c} was -0.76% with sitagliptin and -0.64% with glipizide (Per-Protocol Analysis). In this study, the efficacy and safety profile of sitagliptin at 25 or 50 mg once daily was generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycemia in the sitagliptin group (6.2%) was significantly lower than that in the glipizide group (17.0%).

Another study comparing sitagliptin at 25 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in 129 patients with ESRD who were on dialysis (64 patients on sitagliptin; and 65 patients on glipizide).

Table 27 – Summary of Study Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P073	Multicentre, randomized, double-blind, active-controlled	Sitagliptin 25 mg/day or Glipizide 2.5 to 20 mg/day Oral 54 weeks	129	59.5 years (38–83)	Male: 77 Female: 52

After 54 weeks, the mean reduction from baseline in HbA_{1c} was -0.72% with sitagliptin and -0.87% with glipizide. In this study, the efficacy and safety profile of sitagliptin at 25 mg once daily was

generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycemia was not significantly different between the treatment groups (sitagliptin: 6.3%; glipizide: 10.8%).

In a study involving 91 patients with type 2 diabetes and chronic renal impairment (creatinine clearance <50 mL/min), the safety and tolerability of treatment with sitagliptin at 25 or 50 mg once daily were generally similar to placebo.

Table 28 – Summary of Study Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)
P028	Multicentre, randomized, double-blind, placebo- and active- controlled	Sitagliptin 25 or 50 mg/day or Placebo for 12 weeks followed by glipizide 2.5 to 20 mg/day for 42 weeks Oral 54 weeks	91	67.9 years (41–92)

TECOS Cardiovascular Safety Study

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a randomized double-blind, placebo-controlled, parallel-group, event-driven, multicentre study in patients with type 2 diabetes mellitus (HbA_{1C} ≥6.5 to 8.0%) and established vascular disease (coronary artery disease, ischemic cerebrovascular disease, atherosclerotic peripheral artery disease). The study included 14,671 (70.7% male, 29.3% female) patients in the intention-to-treat population who received sitagliptin (N=7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥30 and <50 mL/min/1.73 m^2) or placebo (N=7,339) added to usual care targeting regional standards for HbA_{1C} and CV risk factors. The median duration of treatment was 31 months and the median duration of follow-up was 36 months. Patients with an eGFR <30 mL/min/1.73 m^2 were not to be enrolled in the study. The study population included 10,863 patients with coronary artery disease, 3,588 patients with cerebrovascular disease, 2,433 patients with peripheral artery disease, 2,643 patients with prior congestive heart failure (including 373 with New York Heart Association [NYHA] class 3 or higher), 2,004 patients ≥75 years of age, and 3,324 patients with renal impairment (eGFR <60 mL/min/1.73 m^2).

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, non- fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina. Secondary cardiovascular endpoints included a composite of the first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke; as well as first occurrence of the following independent CV endpoints: cardiovascular death, myocardial infarction (fatal + non-fatal), stroke (fatal + non-fatal), hospitalization for unstable angina, hospitalization for heart failure, and all-cause mortality. A composite endpoint of first occurrence of death due to heart

failure or hospitalization for congestive heart failure was also assessed

Sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of death or hospitalization for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes. Superiority to placebo was not demonstrated for any endpoint (Table 29).

Table 29 -Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes Censored at the End of Follow-up (Intention-to-Treat Population)

	Sitagliptin (N=7,332)		Placebo (N=7,339)		Hazard Ratio (95% CI)	p-value†
	Subjects with Events N (%)	Incidence Rate per 100 Patient-Years*	Subjects with Events N (%)	Incidence Rate per 100 Patient-Years*		
Primary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2	0.98 (0.89, 1.08)	<0.001
Secondary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke)	745 (10.2)	3.6	746 (10.2)	3.6	0.99 (0.89, 1.10)	<0.001
Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89, 1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81, 1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79, 1.19)	0.760
Hospitalization for unstable angina	116 (1.6)	0.5	129 (1.8)	0.6	0.90 (0.70,	0.419

	Sitagliptin (N=7,332)		Placebo (N=7,339)		Hazard Ratio (95% CI)	p-value†
	Subjects with Events N (%)	Incidence Rate per 100 Patient-Years*	Subjects with Events N (%)	Incidence Rate per 100 Patient-Years*		
					1.16)	
Death from any cause	547 (7.5)	2.5	537 (7.3)	2.5	1.01 (0.90, 1.14)	0.875
Hospitalization for heart failure‡	228 (3.1)	1.1	229 (3.1)	1.1	1.00 (0.83, 1.20)	0.983
Death due to heart or failure hospitalization for heart failure‡	237 (3.2)	1.1	240 (3.3)	1.1	0.99 (0.83, 1.18)	0.909

* Incidence rate per 100 patient-years is calculated as 100 × (total number of patients with ≥1 event during eligible exposure period per total patient-years of follow-up).

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

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

14.3 Comparative Bioavailability Studies

A double-blind, randomized, two-treatment, two-sequence, two-period, crossover bioequivalence study of PRZ-SITAGLIPTIN tablets 100 mg (Pharmaris Canada Inc.) and JANUVIA tablets 100 mg (Merck Canada Inc.) was conducted in 24 healthy adult male volunteers under fasting conditions. The test and reference products were administered as single oral doses of 1 x 100 mg sitagliptin. The results from 22 volunteers that completed the study are summarized in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Sitagliptin (1 x 100 mg sitagliptin) Geometric Mean Arithmetic Mean (%CV)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	4032.76 4064.86 (12.76%)	4041.89 4081.34 (14.23%)	99.9	98.1 - 101.7
AUC_I (ng·h /mL)	4111.57 4145.48 (13.1)	4118.85 4160.10 (14.5)	100.0	98.2 - 101.8
C_{max} (ng/mL)	430.04 441.38 (23.2)	454.85 467.023 (23.3)	94.1	87.4 - 101.2
T_{max} (h) [3]	3.33 (0.67 - 5.00)	2.33 (1.00 - 5.00)		
$T_{1/2}$ (h) [4]	8.59 (11.93)	8.59 (11.06)		

[1] PRZ-SITAGLIPTIN (sitagliptin, as sitagliptin phosphate monohydrate) tablets 100 mg (Pharmaris Canada Inc.)

[2] JANUVIA® (sitagliptin, as sitagliptin phosphate monohydrate) tablets 100 mg (Merck Canada Inc.)

[3] Expressed as the median (range) only

[4] Expressed as the arithmetic mean (%CV) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

The approximate LD50 of sitagliptin given orally to rats is >3000 mg/kg (maximum dose tested). This dose is equivalent to ≥200 times the human exposure based on the recommended daily adult human dose of 100 mg/day. In mice the approximate oral LD50 of sitagliptin is 4000 mg/kg. This dose is equivalent to >385 times the human exposure based on recommended daily adult human dose of 100 mg/day.

Chronic Toxicity

The toxicity potential of sitagliptin was evaluated in a series of repeated dose toxicity studies of up to 53 weeks in dogs and up to 27 weeks in rats. In dogs administered sitagliptin orally at dosages of 2, 10 and 50 mg/kg/day, the no-observed effect level was 10 mg/kg/day (up to 6 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Treatment-related physical signs observed in the 50 mg/kg/day group included open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture. These signs were transient, slight in degree, and occurred with decreased incidence during the course of the study. In addition, very slight to slight skeletal muscle degeneration was observed histologically in the 14- and 27-week toxicity studies at the 50 mg/kg/day dose. However, no skeletal muscle degeneration was found in the 53-week toxicity study, indicating the lack of reproducibility or progression of this change with increased duration of treatment. The 50 mg/kg/day dose in dogs resulted in systemic exposure values 26 times the human exposure at the recommended daily adult human dose of 100 mg/day. In rats, sitagliptin administered orally at dosages of up to 180 mg/kg/day (up to 23 times the human exposure based on the recommended daily adult human dose of 100 mg/day), no significant toxicity was observed. The only drug-related effect observed was post- dose salivation, likely related to poor palatability of the drug, at doses of 60 mg/kg/day and 180 mg/kg/day.

The treatment-related changes noted in animals do not suggest any clinical concerns at the recommended therapeutic dosages in humans.

Carcinogenicity

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 hepatic adenomas and carcinomas in the high-dose males and hepatic carcinomas in the high-dose females. This dose in rats results in approximately 58 times the human exposure based on the recommended daily adult human dose of 100 mg/day. This dose level was associated with hepatotoxicity in rats. The no-observed effect level for induction of hepatic neoplasia was 150 mg/kg/day, approximately 19-fold the human exposure at the 100-mg recommended dose. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumors in rats was likely secondary to chronic hepatic toxicity at this high dose. The clinical significance of these findings for humans is unknown.

A two-year carcinogenicity study was conducted in male and female mice at oral doses of 50, 125, 250, and 500 mg/kg/day. Sitagliptin did not increase tumor incidence in mice in any organ at doses up to 500 mg/kg/day (approximately 68 times the human exposure based on the recommended daily adult human dose of 100 mg/day).

Genotoxicity:

Sitagliptin was not mutagenic or clastogenic in a battery of genetic toxicology studies, including the Ames bacterial assay (microbial mutagenesis test), Chinese hamster ovary cells (CHO cells) chromosome aberration assay, an *in vitro* cytogenetics assay using CHO cells, an *in vitro* rat hepatocyte DNA alkaline elution assay (an assay which measures the compound's ability to induce single strand breaks in DNA), and an *in vivo* micronucleus assay.

Reproductive and Developmental Toxicology:

No adverse effects upon fertility were observed in male and female rats given sitagliptin orally at doses up to 1000 mg/kg daily (up to approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day) prior to and throughout mating.

Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg or in rabbits given up to 125 mg/kg during organogenesis (up to 32 and 22 times the human exposure based on the recommended daily adult human dose of 100 mg/day). A slight, treatment-related increased incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) was observed in the offspring of rats at oral doses of 1000 mg/kg/day (approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day). The no-observed effect level for developmental effects was 250 mg/kg/day (32 times the human exposure based on the recommended daily adult human dose of 100 mg/day).

Treatment-related decreases in the mean preweaning body weight of both sexes and postweaning body weight gain of male animals was observed in offspring of rats at oral doses of 1000 mg/kg.

17 SUPPORTING PRODUCT MONOGRAPHS

JANUVIA Product Monograph (Control #242950) by Merk Canada Inc. Date of revision: July 27, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]PRZ-SITAGLIPTIN
sitagliptin (as sitagliptin phosphate monohydrate)
tablets

Read this carefully before you start taking **PRZ-SITAGLIPTIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PRZ-SITAGLIPTIN**.

What is PRZ-SITAGLIPTIN used for?
PRZ-SITAGLIPTIN is used in addition to diet and exercise to improve blood sugar levels in adult patients with type 2 diabetes mellitus:

- alone in patients who cannot take metformin
- in combination with metformin
- in combination with metformin and a sulfonylurea (e.g. glyburide, gliclazide or glimepiride)
- in combination with premixed or long/intermediate acting insulin (with or without metformin)
- in combination with pioglitazone (with or without metformin)

How does PRZ-SITAGLIPTIN work?
PRZ-SITAGLIPTIN contains the medicinal ingredient sitagliptin which belongs to a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors). PRZ-SITAGLIPTIN helps to improve the levels of insulin when blood sugar level is high, especially after a meal. PRZ-SITAGLIPTIN also helps to decrease the amount of sugar made by the body. PRZ-SITAGLIPTIN is unlikely to cause low blood sugar (**hypoglycemia**).

What are the ingredients in PRZ-SITAGLIPTIN?
Medicinal ingredients: sitagliptin phosphate monohydrate

Non-medicinal ingredients: Calcium hydrogen phosphate, croscarmellose sodium, instacoat pink, instacoat beige, instacoat peach, purified water, microcrystalline cellulose, and sodium stearyl fumerate .

PRZ-SITAGLIPTIN comes in the following dosage forms:
Tablets: 25 mg, 50 mg, 100 mg

Do not use PRZ-SITAGLIPTIN if:

- you are allergic (hypersensitive) to sitagliptin or any of the other ingredients in PRZ-SITAGLIPTIN.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PRZ-SITAGLIPTIN. Talk about any health conditions or problems you may have,

including if you:

- have or have had pancreatitis (inflammation of the pancreas);
- have risk factors for pancreatitis such as:
  - gallstones (solid particles that form in the gall bladder),
  - a history of alcoholism,
  - high triglyceride levels;
- have type 1 diabetes;
- have or have had diabetic ketoacidosis (increased ketones in the blood or urine);
- have or have had kidney problems;
- have liver problems;
- had an organ transplant;
- have human immunodeficiency syndrome (HIV);
- are pregnant or plan to become pregnant; PRZ-SITAGLIPTIN is not recommended for use during pregnancy;
- are breastfeeding or plan to breastfeed. It is not known if PRZ-SITAGLIPTIN passes into breast milk.

Other warnings you should know about:

Serious Skin Reactions and Pancreatitis:

- **PRZ-SITAGLIPTIN can cause serious side effects, including:**
  - **Pancreatitis** (inflammation of the pancreas) which can be life-threatening and cause death.
  - **Serious Skin Reactions** called **Stevens-Johnson syndrome** and **bullous pemphigoid**. These reactions can happen after your first dose or up to 3 months after you start PRZ-SITAGLIPTIN.

  See the **Serious side effects and what to do about them** table, below for more information on these and other serious side effects.

Hypoglycemia (low blood sugar):

- When PRZ-SITAGLIPTIN is used with metformin and a sulfonylurea medicine or with insulin (with or without metformin), **hypoglycemia** (low blood sugar) can occur. Lower doses of the sulfonylurea medicine or insulin may be required while you take PRZ-SITAGLIPTIN. You should use caution when driving or using machines if you are taking PRZ-SITAGLIPTIN with a sulfonylurea medicine or with insulin.

Blood Tests:

PRZ-SITAGLIPTIN may cause abnormal blood tests. Your healthcare professional will do blood tests before you start PRZ-SITAGLIPTIN and while you are taking it. They may check your blood sugar, liver function and how well your kidneys are working. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

How to take PRZ-SITAGLIPTIN:

- Take PRZ-SITAGLIPTIN exactly as your healthcare professional tells you to.
- PRZ-SITAGLIPTIN can be taken with or without food.

Usual adult dose:
100 mg once daily. Your healthcare professionals may adjust your dose if you have kidney problems.

Overdose:

If you think you, or a person you are caring for, have taken too much PRZ-SITAGLIPTIN, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose of PRZ-SITAGLIPTIN to make up for a missed dose.

What are possible side effects from using PRZ-SITAGLIPTIN?
These are not all the possible side effects you may feel when taking PRZ-SITAGLIPTIN. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Stuffy or runny nose
- Sore throat
- Vomiting
- Constipation
- Headache
- Joint pain
- Muscle aches
- Arm or leg pain
- Back pain
- Itching
- Blisters

Serious side effects and what to do about them			
Symptoms / Effects	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Hypoglycemia (low blood sugar – when used with metformin and a sulfonylurea, or when used with insulin with or without metformin): shaking, sweating, rapid heartbeat, change in vision, hunger, headache and change in mood**.**		x	

Serious side effects and what to do about them			
Symptoms / Effects	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Pancreatitis (inflammation of the pancreas): prolonged severe stomach pain and possible vomiting.			x
Allergic reactions: rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.			x
Serious skin reactions including Stevens-Johnson syndrome, bullous pemphigoid: blisters or breakdown of your skin.		x	
Acute kidney failure (sometimes requiring dialysis): nausea, loss of appetite and weakness, pass little or no urine, breathlessness.			x
VERY RARE			
Rhabdomyolysis (breakdown of damaged muscle): muscle spasms, weakness, red-brown (tea-coloured) urine.			x

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Preserve in well-closed containers. Store at room temperature (15°C to 30°C).
Keep out of reach and sight of children.

If you want more information about PRZ-SITAGLIPTIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html or the Pharmaris Canada website www.pharmaris.com or by calling Pharmaris Canada at 1-866-913-7955.

This leaflet was prepared by Pharmaris Canada Inc.

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