PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-SITAGLIPTIN/METFORMIN XR

Sitagliptin (as sitagliptin phosphate monohydrate) and metformin hydrochloride modified-release

Tablets, 50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg, Oral

Combinations of oral blood glucose lowering drugs

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RECENT MAJOR LABEL CHANGES

1 Indications	02/2022
4 Dosage and Administration	02/2022
7 Warnings and Precautions	02/2022

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

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

- APO-SITAGLIPTIN/METFORMIN XR (sitagliptin and metformin hydrochloride modified-release tablets) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on metformin or in patients already being treated with the combination of sitagliptin and metformin.
- **Add-on combination**: APO-SITAGLIPTIN/METFORMIN XR are indicated for use as a triple combination therapy in adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with:
    - sulfonylurea,
    - premixed or long/intermediate acting insulin
    - pioglitazone

when the existing dual therapy with metformin, 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 APO-SITAGLIPTIN/METFORMIN XR 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):** APO-SITAGLIPTIN/METFORMIN XR should be used with caution in geriatric patients. Sitagliptin and metformin are substantially excreted by the kidney. Because aging can be associated with reduced 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, 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, and Special Populations).

2 CONTRAINDICATIONS

- Unstable and/or insulin-dependent (type 1) diabetes mellitus.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma.
- In patients with a history of lactic acidosis, irrespective of precipitating factors (see 7 WARNINGS AND PRECAUTIONS).

- In the presence of severe renal impairment [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2)], end-stage renal disease, in patients on dialysis or when renal function is not known (see 7 WARNINGS AND PRECAUTIONS).
- In excessive alcohol intake, acute or chronic.
- In patients suffering from severe hepatic dysfunction, since severe hepatic dysfunction has been associated with some cases of lactic acidosis, APO-SITAGLIPTIN/METFORMIN XR should not be used in patients with clinical or laboratory evidence of hepatic disease.
- In cases of cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia.
- During stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.
- In patients suffering from severe dehydration or shock.
- Known hypersensitivity to sitagliptin, metformin 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.
- During pregnancy and breastfeeding (see 7 WARNINGS AND PRECAUTIONS, Special populations).
- During period around administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see 7 WARNINGS AND PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Lactic Acidosis

- Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with APO-SITAGLIPTIN/METFORMIN XR (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism – Lactic Acidosis).
- Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking APO-SITAGLIPTIN/METFORMIN XR, since alcohol intake potentiates the effect of metformin on lactate metabolism (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism – Lactic Acidosis).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The dosage of APO-SITAGLIPTIN/METFORMIN XR should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin hydrochloride. Dose escalation should be gradual to reduce the gastrointestinal side effects associated with metformin use. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin-containing products in patients with renal impairment. Maximum daily dose of sitagliptin and metformin, as single components, in patients with an eGFR ≥30 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2 is 50 mg and 1000 mg, respectively.
- There have been reports of incompletely dissolved sitagliptin and metformin hydrochloride modified-release tablets being eliminated in the feces. If a patient reports seeing tablets in feces, the healthcare provider should assess adequacy of glycemic control (see PATIENT MEDICATION INFORMATION). If glycemic control is found to be reduced, alternative treatments should be considered.
- **Concomitant Use with Insulin or an Insulin Secretagogue (e.g., Sulfonylurea)**

  When APO-SITAGLIPTIN/METFORMIN XR is used as add-on therapy with insulin or an insulin secretagogue (e.g., sulfonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycemia (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).
- **Concomitant Use with Medication(s) that May Decrease Renal Function**

  Caution should be exercised when using concomitant medication(s) that may decrease renal function (like diuretics, particularly loop diuretics) or may interfere with the disposition of metformin, such as cationic drugs, that are eliminated by renal tubular secretion, due to the increased risk of developing lactic acidosis during co-administration (see 9 DRUG INTERACTIONS).

4.2 Recommended Dose and Dosage Adjustment

For the following dosage strengths of APO-SITAGLIPTIN/METFORMIN XR:

- 50 mg sitagliptin/500 mg metformin hydrochloride modified release tablet
- 50 mg sitagliptin/1000 mg metformin hydrochloride modified release tablet

Two APO-SITAGLIPTIN/METFORMIN XR tablets should be taken orally once a day with a meal preferably in the evening. Administration of APO-SITAGLIPTIN/METFORMIN XR with food enhances plasma concentrations of metformin. The two tablets should be taken one immediately after the other and to preserve the modified-release properties, the tablets must not be split, broken crushed, or chewed before swallowing.

For the following dosage strength of APO-SITAGLIPTIN/METFORMIN XR:

- 100 mg sitagliptin/1000 mg metformin hydrochloride modified release tablet

One single APO-SITAGLIPTIN/METFORMIN XR tablet should be taken orally once a day with a meal preferably in the evening. Administration of APO-SITAGLIPTIN/METFORMIN XR with food enhances plasma concentrations of metformin. To preserve the modified-release properties, the tablets must not be split, broken crushed, or chewed before swallowing.

In patients on metformin (alone or in combination with a sulfonylurea, pioglitazone, or insulin), the recommended total daily dose of APO-SITAGLIPTIN/METFORMIN XR is 100 mg sitagliptin and the nearest therapeutically appropriate dose of metformin already being taken.

In patients already treated with sitagliptin and metformin, switching to APO-SITAGLIPTIN/METFORMIN XR may be initiated at the dose of sitagliptin and metformin already being taken.

Renal Impairment: Renal function must be assessed prior to initiation of APO-SITAGLIPTIN/METFORMIN XR and periodically thereafter because there is a dosage adjustment based upon renal function. In patients with eGFR <60 mL/min/1.73m^2, more intensive monitoring for glycemic biomarkers, renal biomarkers and signs and symptoms of renal dysfunction is recommended especially if the eGFR is less than 45 mL/min/1.73 m^2 (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

APO-SITAGLIPTIN/METFORMIN XR is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis (see 2 CONTRAINDICATIONS).

No dosage adjustment for APO-SITAGLIPTIN/METFORMIN XR is necessary in patients with mild (eGFR ≥60 mL/min/1.73 m^2 to <90 mL/min/1.73 m^2) to moderate renal impairment (eGFR ≥45 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2).

Initiation of APO-SITAGLIPTIN/METFORMIN XR in patients with an eGFR ≥30 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2 is not recommended. In patients taking APO-SITAGLIPTIN/METFORMIN XR whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy and limit dose of the sitagliptin component to 50 mg once day:

- APO-SITAGLIPTIN/METFORMIN XR 50 mg/500 mg – 1 tablet once daily
- APO-SITAGLIPTIN/METFORMIN XR 50 mg/1000 mg – 1 tablet once daily

Discontinue APO-SITAGLIPTIN/METFORMIN XR if the patient's eGFR later falls below 30 mL/min/1.73 m^2.

Discontinuation for iodinated contrast imaging procedures:

Discontinue APO-SITAGLIPTIN/METFORMIN XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR ≥30 to <60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra- arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart APO-SITAGLIPTIN/METFORMIN XR if renal function is acceptable and found to be stable (see 7 WARNINGS AND PRECAUTIONS).

Hepatic Impairment: APO-SITAGLIPTIN/METFORMIN XR is contraindicated in patients with severe hepatic impairment and should not be used in patients with clinical or laboratory evidence of hepatic disease (see 2 CONTRAINDICATIONS). Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis (see 7 WARNINGS AND PRECAUTIONS).

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

Geriatrics (≥65 years of age): APO-SITAGLIPTIN/METFORMIN XR should be used with caution in patients 65 years and older. Regular assessment of renal function is necessary. Metformin and sitagliptin are excreted by the kidneys, and elderly patients are more likely to have decreased renal function associated with aging and be at risk of developing lactic acidosis (see 7 WARNINGS AND PRECAUTION, Special Populations).

4.4 Administration

APO-SITAGLIPTIN/METFORMIN XR should be taken orally with meals.

4.5 Missed Dose

If a dose of APO-SITAGLIPTIN/METFORMIN XR is missed, it should be taken as soon as the patient remembers. If he/she does not remember until it is time for the next dose, the missed dose should be skipped and returned to the regular schedule. A double dose of APO-SITAGLIPTIN/METFORMIN XR should not be taken at the same time.

5 OVERDOSAGE

Sitagliptin

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.

Metformin hydrochloride

Available information concerning treatment of a massive overdosage of metformin hydrochloride is very limited. It would be expected that adverse reactions of a more intense

character including epigastric discomfort, nausea and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded. The drug should be discontinued and proper supportive therapy instituted.

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see 7 WARNINGS AND PRECAUTIONS). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Pancreatitis may occur in the context of a metformin overdose (see 7 WARNINGS AND PRECAUTIONS).

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	Modified-release Tablets: immediate release sitagliptin (as sitagliptin phosphate monohydrate) / extended release metformin hydrochloride 50 mg§500 mg 50 mg§/1000 mg 100 mg§§/1000 mg	Colloidal silicon dioxide, hypromellose, indigotine AL Lake 12-14%, magnesium stearate, methyl cellulose, polyethylene glycol, polyvinyl alcohol, propyl gallate, talc and titanium dioxide. APO-SITAGLIPTIN/METFORMIN XR, 50 mg/1000 mg tablet contains the additional inactive ingredient yellow ferric oxide.

§ 64.25 mg of sitagliptin phosphate monohydrate

§§ 128.5 mg of sitagliptin phosphate monohydrate

APO-SITAGLIPTIN/METFORMIN XR consists of an extended-release metformin core tablet coated with an immediate release layer of sitagliptin. The sitagliptin layer is coated with a soluble polymeric film that provides taste masking.

Tablets APO-SITAGLIPTIN/METFORMIN XR, 50 mg/500 mg, are light blue, biconvex, oval shaped, bevelled edged coated tablets. Engraved "SI-ME" on one side, "APO" on the other side. They are supplied in bottles of 100.

Tablets APO-SITAGLIPTIN/METFORMIN XR, 50 mg/1000 mg, are green, biconvex, oval shaped, bevelled edged coated tablets. Engraved "SI-ME" on one side, "APO" on the other side. They are supplied in bottles of 100.

Tablets APO-SITAGLIPTIN/METFORMIN XR, 100 mg/1000 mg, are blue, biconvex, oval shaped, bevelled edged coated tablets. Engraved "SI-ME" on one side, "APO" on the other side. They are supplied in bottles of 100.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

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

Cardiovascular

Hypoxic States:

Metformin hydrochloride

Cardiovascular collapse (shock) from whatever cause (e.g., acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia) have been associated with lactic acidosis and may also cause prerenal azotemia (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism). When such events occur in patients on APO-SITAGLIPTIN/METFORMIN XR therapy, the drug should be promptly discontinued.

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 (see 7 WARNINGS AND PRECAUTIONS). When APO-SITAGLIPTIN/METFORMIN XR is used in combination with a sulfonylurea or in combination with insulin patients should

be advised to take precautions to avoid hypoglycaemia while driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Hypoglycemia:

Sitagliptin

When sitagliptin and metformin were used in combination with a sulfonylurea or in combination with insulin, the incidence of hypoglycemia was increased over that of placebo and metformin used in combination with a sulfonylurea or in combination with insulin (see 8 ADVERSE REACTIONS). To reduce the risk of hypoglycemia associated with these regimens, a lower dose of sulfonylurea or insulin may be considered (see 4 DOSAGE AND ADMINISTRATION).

Metformin hydrochloride

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

Hypothyroidism:

Metformin hydrochloride

Metformin induces a reduction in thyrotropin (thyroid stimulating hormone (TSH) levels in patients with treated or untreated hypothyroidism (see 8 ADVERSE REACTIONS). Regular monitoring of TSH levels is recommended in patients with hypothyroidism (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Studies have shown that metformin reduces plasma TSH levels, often to subnormal levels, when it is administered to patients with untreated hypothyroidism or to hypothyroid patients effectively treated with Levothyroxine. The metformin-induced reduction of plasma TSH levels is not observed when metformin is administered to patients with normal thyroid function. Metformin has been suggested to enhance the inhibitory modulation of thyroid hormones on TSH secretion.

Levothyroxine can reduce the hypoglycemic effect of metformin. Careful monitoring of blood glucose levels is recommended in patients with hypothyroidism treated with levothyroxine, especially when thyroid hormone therapy is initiated, changed, or stopped (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 9 DRUG INTERACTIONS).

Lactic Acidosis:

Metformin hydrochloride

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with APO-SITAGLIPTIN/METFORMIN XR when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 mcg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications (see 4 DOSAGE AND ADMINISTRATION).

Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age (see 7 WARNINGS AND PRECAUTIONS, Special Populations). The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin.

In addition, APO-SITAGLIPTIN/METFORMIN XR should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking APO-SITAGLIPTIN/METFORMIN XR, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, APO-SITAGLIPTIN/METFORMIN XR should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. APO-

SITAGLIPTIN/METFORMIN XR should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

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

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

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking APO-SITAGLIPTIN/METFORMIN XR, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hepatic/Biliary/Pancreatic and Renal).

Physicians should instruct their patients to recognize the symptoms which could be a signal of the onset of lactic acidosis. If acidosis of any kind develops, APO-SITAGLIPTIN/METFORMIN XR should be discontinued immediately and the patient should be immediately hospitalized.

Change in Clinical Status of Previously Controlled Diabetes Patients:

Metformin hydrochloride

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

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 APO-SITAGLIPTIN/METFORMIN XR, therapeutic alternatives should be considered.

Metformin hydrochloride

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold APO-SITAGLIPTIN/METFORMIN XR and temporarily administer insulin. APO-SITAGLIPTIN/METFORMIN XR may be reinstituted after the acute episode is resolved.

Vitamin B_{12} Levels:

Metformin hydrochloride

Impairment of vitamin B_{12} absorption has been reported in some patients treated with metformin. Therefore, measurements of serum vitamin B_{12} are advisable at least every one to two years in patients on long-term treatment with APO-SITAGLIPTIN/METFORMIN XR.

A decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, is observed in approximately 7% of patients receiving metformin in controlled clinical trials of 28 weeks duration. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on APO-SITAGLIPTIN/METFORMIN XR and any apparent abnormalities should be appropriately investigated and managed (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels.

Long-term treatment with metformin has been associated with a decrease in serum vitamin B_{12} levels which may cause peripheral neuropathy. Serious cases of peripheral neuropathy have been reported with metformin treatment, one of the components of APO-SITAGLIPTIN/METFORMIN XR, in the context of vitamin B_{12} deficiency (see 8 ADVERSE REACTIONS). Monitoring of serum vitamin B_{12} levels is recommended (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Hematologic

Metformin hydrochloride

Serious cases of metformin-induced hemolytic anemia, some with fatal outcome, have been reported (see 8 ADVERSE REACTIONS). Two mechanisms were described for the metformin-induced immune hemolytic anemia; formation of an antibody against the erythrocyte-metformin complex and autoantibody formation. Monitoring of hematologic parameters is recommended (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Hepatic/Biliary/Pancreatic

Hepatic: APO-SITAGLIPTIN/METFORMIN XR is contraindicated in patients with severe hepatic dysfunction and should not be used in patients with clinical or laboratory

evidence of hepatic disease (see 2 CONTRAINDICATIONS).

Sitagliptin

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 10 CLINICAL PHARMACOLOGY).

Metformin hydrochloride

Impaired hepatic function has been associated with some cases of lactic acidosis.

Pancreatitis:

Sitagliptin

There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin, one of the components of APO-SITAGLIPTIN/METFORMIN XR. 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 sitagliptin patients compared to none in the placebo group. After initiation of APO-SITAGLIPTIN/METFORMIN XR, patients should be observed carefully for signs and symptoms of pancreatitis.

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

Metformin hydrochloride

Serious cases of pancreatitis have been reported in patients receiving metformin (see 8 ADVERSE REACTIONS). The reported pancreatitis cases occurred either in the context of an acute metformin overdose (see 5 OVERDOSAGE) or in patients receiving therapeutic doses of metformin with concurrent renal failure and/or lactic acidosis, indicating metformin accumulation.

Immune

Hypersensitivity Reactions:

Sitagliptin

There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of APO-SITAGLIPTIN/METFORMIN XR. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue APO-SITAGLIPTIN/METFORMIN XR, assess for other potential causes for the event, and institute alternative treatment for diabetes (see 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS).

Immunocompromised Patients:

Sitagliptin

A dose-related mean decrease in absolute lymphocyte count was observed with other dipeptidyl peptidase 4 (DPP-4) inhibitors. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of sitagliptin, a component of APO-SITAGLIPTIN/METFORMIN XR, 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 APO-SITAGLIPTIN/METFORMIN XR treatment should be monitored by periodic measurements of blood glucose and HbA_{1c} levels.

Hematology: Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) should be performed, regularly. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B_{12} deficiency should be excluded. Periodic measurements of serum vitamin B_{12} levels should be performed in patients on long-term treatment with APO-SITAGLIPTIN/METFORMIN XR, especially in patients with anemia or neuropathy (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

A close monitoring of the International Normalized Ratio (INR) is recommended in patients concurrently administering metformin and phenprocoumon or other antivitamin K anticoagulants (see 9 DRUG INTERACTIONS).

Hypothyroidism: Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism.

For hypothyroid patients treated with levothyroxine, careful monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated, changed, or stopped (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, and 9 DRUG INTERACTIONS).

Renal Function: APO-SITAGLIPTIN/METFORMIN XR is contraindicated in patients with an estimated glomerular rate (eGFR) <30 mL/min/1.73 m^2 (see 2 CONTRAINDICATIONS). Renal function must be assessed prior to initiation of APO-SITAGLIPTIN/METFORMIN XR and periodically thereafter, with more frequent monitoring in patients whose eGFR decreases to less than 60 mL/min/1.73 m^2 (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 (see 9 DRUG INTERACTIONS).

Neurologic

Metformin hydrochloride

Serious cases of metformin-induced encephalopathy have been reported (see 8 ADVERSE REACTIONS). Some of these cases were reported without association with lactic acidosis, hypoglycemia, or renal impairment.

Peri-Operative Considerations

Metformin hydrochloride

APO-SITAGLIPTIN/METFORMIN XR therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids). APO-SITAGLIPTIN/METFORMIN XR should be discontinued 2 days before surgical intervention and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as acceptable and found to be stable (see 4 DOSAGE AND ADMINISTRATION).

Renal

APO-SITAGLIPTIN/METFORMIN XR is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) (see 2 CONTRAINDICATIONS).

Before initiation of APO-SITAGLIPTIN/METFORMIN XR therapy and regularly thereafter, renal function must be assessed. In patients with eGFR less than 60 mL/min/1.73m^2, more intensive monitoring for glycemic and renal biomarkers and signs and symptoms of renal dysfunction is recommended, especially if the eGFR is less than 45 mL/min/1.73 m^2 (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 4 DOSAGE AND ADMINISTRATION).

In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and APO-SITAGLIPTIN/METFORMIN XR discontinued if evidence of renal impairment is present.

Special caution should be exercised in situations where renal function may become impaired, for example in the elderly, in the case of dehydration when initiating antihypertensive therapy or diuretic therapy or when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). Therefore, consider more frequent monitoring of patients.

Sitagliptin

Sitagliptin is renally excreted. Renal adverse events, including acute renal failure, have been observed during clinical trials and post-marketing use of sitagliptin, a component of APO-SITAGLIPTIN/METFORMIN XR, in patients with and without known risk factors (see 8 ADVERSE REACTIONS).

Metformin hydrochloride

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

Use of concomitant medications that may affect renal function or metformin disposition: Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs, that are eliminated by renal tubular secretion (see 9 DRUG INTERACTIONS) should be used with caution. The concomitant use of APO-SITAGLIPTIN/METFORMIN XR with these specific drugs may increase the risk of metformin-associated lactic acidosis and therefore, consider more frequent monitoring of patients.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials):

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see 2 CONTRAINDICATIONS). Therefore, in patients with an eGFR ≥ 30 to < 60 mL/min/1.73 m^2, in patients with a history of hepatic impairment, alcoholism, or heart failure, or in patients who will be administered intra-arterial iodinated contrast, APO-SITAGLIPTIN/METFORMIN XR should be discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be acceptable and stable (see 4 DOSAGE AND ADMINISTRATION).

Reproductive Health: Female and Male Potential

See 2 CONTRAINDICATIONS and 7.1.1 SPECIAL POPULATIONS, Pregnant Women

Skin

Sitagliptin

With other members of this class, DPP-4 inhibitors, 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 with sitagliptin, a component of APO-SITAGLIPTIN/METFORMIN XR. 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 DPP-4 inhibitors, including sitagliptin, a component of APO-SITAGLIPTIN/METFORMIN XR. 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 APO-SITAGLIPTIN/METFORMIN XR. If bullous pemphigoid is suspected, APO-SITAGLIPTIN/METFORMIN XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

7.1 Special Populations

7.1.1 Pregnant Women

APO-SITAGLIPTIN/METFORMIN XR is contraindicated in pregnancy (see 2 CONTRAINDICATIONS). There are no adequate and well-controlled studies in pregnant women with sitagliptin and metformin hydrochloride modified-release tablets or their individual components; therefore, the safety of APO-SITAGLIPTIN/METFORMIN XR in pregnant women is not known. When pregnancy is detected, APO-SITAGLIPTIN/METFORMIN XR should be discontinued.

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

Sitagliptin

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 sitagliptin in pregnant women is not known.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two and six times the maximum recommended human daily dose on a body surface area basis.

Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Because animal reproduction studies are not always predictive of human response, APO-SITAGLIPTIN/METFORMIN XR is contraindicated during pregnancy (see 2 CONTRAINDICATIONS).

7.1.2 Breast-feeding

APO-SITAGLIPTIN/METFORMIN XR is contraindicated during breast-feeding (see 2 CONTRAINDICATIONS). No studies in lactating animals have been conducted with the combined components of sitagliptin and metformin hydrochloride modified-release tablets. Both sitagliptin and metformin are present in the milk of lactating rats. Metformin hydrochloride is also excreted into human breast milk in very small amounts but it is unknown if sitagliptin is excreted in human milk. Therefore, APO-SITAGLIPTIN/METFORMIN XR 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 APO-SITAGLIPTIN/METFORMIN XR 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): Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, APO-SITAGLIPTIN/METFORMIN XR should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function (see 7 WARNINGS AND PRECAUTIONS, Renal, and 4 DOSAGE AND ADMINISTRATION).

Sitagliptin

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. Renal function should be assessed prior to initiating dosing and periodically thereafter in geriatric patients (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Sitagliptin

Sitagliptin was generally well tolerated in controlled clinical studies as monotherapy and as part of a combination therapy with metformin or combination therapy with metformin and a sulfonylurea or combination therapy with metformin, insulin and pioglitazone.

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 reaction with sitagliptin as add-on combination therapy with metformin and a sulfonylurea agent or with metformin and insulin was hypoglycemia.

Metformin hydrochloride

The adverse events most commonly associated with metformin (sitagliptin/metformin) are diarrhea, nausea, and upset stomach. Similar adverse reactions were seen in patients treated with modified-release metformin products. Lactic acidosis is a rare, but serious side effect. Lactic acidosis is fatal in approximately 50% of cases.

Lactic Acidosis: very rare (<1/10, 000 and isolated reports) (see 7 WARNINGS AND PRECAUTIONS and 5 OVERDOSAGE).

Gastrointestinal Reactions: very common (>1/10): Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to metformin and are approximately 30% more frequent in patients on metformin monotherapy than in placebo-treated patients, particularly during initiation of metformin therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful.

Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take metformin (metformin hydrochloride) with meals (see 4 DOSAGE AND ADMINISTRATION).

Because significant diarrhea and/or vomiting can cause dehydration and prerenal azotemia, metformin should be temporarily discontinued, under such circumstances.

For patients who have been stabilized on metformin, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded.

Special Senses: common (≥1/100): During initiation of metformin therapy complaints of taste disturbance are common, i.e. metallic taste.

Dermatologic Reactions: very rare (<1/10,000 and isolated reports): The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for metformin monotherapy and to sulfonylurea for metformin /sulfonylurea therapy. Reports of skin reactions such as erythema, pruritus, and urticaria are very rare.

Hematologic: Decrease of vitamin B_{12} absorption with decrease of serum levels

during long- term use of metformin is rare (≥1/10,000 and <1/1,000). Consideration of such etiology is recommended if a patient presents with megaloblastic anemia.

Hepatic: very rare (<1/10,000 and isolated reports): Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation has been documented in isolated reports.

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.

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 2.

Table 2 – 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)
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)

	Number of patients (%)	
Body system/Organ class **Adverse event**	**Sitagliptin 100 mg + Metformin n=464**	**Placebo + Metformin n=237**
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		
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)

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 3.

Table 3 – 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)
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 4. The overall incidence of adverse events with sitagliptin was higher than with placebo, in part related to higher incidence of hypoglycemia (see 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 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)
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)

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Glimepiride n=116**	**Placebo + Metformin + Glimepiride n=113**
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)
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 to Metformin and Insulin

In a 24-week placebo-controlled study of sitagliptin 100 mg once daily added to ongoing combination treatment with metformin and insulin (sitagliptin, N=229; placebo, N=233), the only adverse experience reported regardless of causality assessment in ≥ 5% of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycemia (sitagliptin 15.3%; placebo 8.2%).

Table 5 – 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 Insulin

	Number of patients (%)	
Body system/Organ class Adverse event	**Sitagliptin 100 mg + Metformin + Insulin n=229**	**Placebo + Metformin + Insulin n=233**
Gastrointestinal Disorders		
Constipation	4 (1.7)	0 (0.0)
Diarrhea	4 (1.7)	4 (1.7)
Nausea	2 (0.9)	4 (1.7)
Vomiting	4 (1.7)	2 (0.9)
General disorders and administration site conditions		
Asthenia	3 (1.3)	1 (0.4)
Fatigue	0 (0.0)	3 (1.3)
Infections and infestations		
Bronchitis	5 (2.2)	4 (1.7)
Gastroenteritis	1 (0.4)	3 (1.3)
Influenza	9 (3.9)	9 (3.9)
Nasopharyngitis	7 (3.1)	7 (3.0)
Respiratory tract infection	3 (1.3)	2 (0.9)
Sinusitis	2 (0.9)	4 (1.7)
Upper respiratory tract infection	8 (3.5)	10 (4.3)
Urinary tract infection	5 (2.2)	5 (2.1)
Viral infection	0 (0.0)	3 (1.3)
Investigations		
Creatinine renal clearance decreased	3 (1.3)	0 (0.0)
Metabolism and nutrition disorders		
Hypoglycemia	35 (15.3)	19 (8.2)
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (0.4)	5 (2.1)
Muscle spasms	0 (0.0)	4 (1.7)
Musculoskeletal pain	2 (0.9)	3 (1.3)
Pain in extremity	4 (1.7)	2 (0.9)
Nervous system disorders		
Dizziness	2 (0.9)	3 (1.3)

	Number of patients (%)	
Body system/Organ class **Adverse event**	**Sitagliptin 100 mg + Metformin + Insulin n=229**	**Placebo + Metformin + Insulin n=233**
Headache	3 (1.3)	2 (0.9)
Respiratory, thoracic and mediastinal disorders		
Cough	2 (0.9)	3 (1.3)

Combination Therapy: Sitagliptin Add-on to Metformin and Pioglitazone

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 6.

Table 6 – 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)
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)

	Number of patients (%)	
Body system/Organ class **Adverse event**	**Sitagliptin 100 mg + Metformin + Pioglitazone n=157**	**Placebo + Metformin + Pioglitazone n=156**
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 metformin and pioglitazone, 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.

8.2.1 Clinical Trial Adverse Reactions - Pediatrics

In clinical trials with sitagliptin and metformin hydrochloride modified-release tablets in pediatric patients aged 10 to 17 years with type 2 diabetes mellitus, the profile of adverse reactions was generally comparable to that observed in adults. In pediatric patients, sitagliptin and metformin hydrochloride modified-release tablets was associated with an increased risk of hypoglycaemia regardless of background insulin therapy.

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)

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, irritable bowel syndrome, reflux esophagitis disease, frequent bowel movements, retching, salivary hypersecretion

General Disorders and Administration Site Conditions: asthenia, chest discomfort, face edema, hunger, irritability, malaise, peripheral edema, pain, pyrexia, thirst, xerosis

Hepatobiliary Disorders: hepatic steatosis

Infections and Infestations: gastric ulcer helicobacter, genital abscess, helicobacter gastritis, localized infection, oropharyngeal candidiasis, 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 tightness, muscle fatigue

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

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

Clinical Trial Findings

Sitagliptin

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 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[1]	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[2]	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]Sitagliptin in Combination with Metformin – Placebo-Controlled Study, see 14 CLINICAL TRIALS

[2]Sitagliptin in Combination with Metformin – Active-Controlled (Sulfonylurea Agent) Study, see 14 CLINICAL TRIALS

In a combination therapy study with insulin and metformin, a greater proportion of patients were observed to have a decrease in hemoglobin ≥1.5 g/dL in the sitagliptin group (6.8%) compared with the placebo group (2.3%).

Metformin hydrochloride

During controlled clinical trials of 29 weeks duration, approximately 9% of patients on metformin monotherapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. Five cases of megaloblastic anemia have been reported with metformin administration and no increased incidence of neuropathy has been observed. However, serious cases of peripheral neuropathy have been reported with metformin treatment in the post-marketing experience in patients with vitamin B_{12} deficiency (see 7 WARNINGS AND PRECAUTIONS and 8ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions).

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.

Blood and lymphatic system disorders: hemolytic anemia, some with a fatal outcome (see 7 WARNINGS AND PRECAUTIONS)

Gastrointestinal disorders: abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see 7 WARNINGS AND PRECAUTIONS), constipation, diarrhea, dry mouth, dyspepsia, flatulence, gastric disorder, gastric ulcer, gastrointestinal disorder, nausea, vomiting

Hepatobiliary disorders: liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, autoimmune hepatitis, drug-induced liver injury, hepatitis (see 7 WARNINGS AND PRECAUTIONS)

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)

Investigations: blood lactic acid increased, reduction of thyrotropin level in patients with treated or untreated hypothyroidism (see 7 WARNINGS AND PRECAUTIONS)

Metabolism and nutrition disorders: lactic acidosis, decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin, weight decreased, decreased appetite, peripheral neuropathy in patients with vitamin B_{12} deficiency, hypomagnesemia in the context of diarrhea (see 7 WARNINGS AND PRECAUTIONS)

Musculoskeletal and connective tissue disorders: arthralgia, myalgia, pain in extremity, back pain, rhabdomyolysis

Nervous system disorders: encephalopathy (see 7 WARNINGS AND PRECAUTIONS), headache

Renal and urinary disorders: worsening renal function, including acute renal failure (sometimes requiring dialysis) (see 7 WARNINGS AND PRECAUTIONS)

Skin and subcutaneous tissue disorder: photosensitivity, erythema, pruritus, rash, skin lesion, urticaria, bullous pemphigoid (see 7 WARNINGS AND PRECAUTIONS)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Pharmacokinetic drug interaction studies with sitagliptin and metformin hydrochloride modified-release tablets have not been performed; however, such studies have been conducted with the individual sitagliptin and metformin components of APO-SITAGLIPTIN/METFORMIN XR.

The simultaneous administration of APO-SITAGLIPTIN/METFORMIN XR and a sulfonylurea could produce a hypoglycemic reaction, especially if they are given in patients already receiving other drugs which, themselves, can potentiate the effect of sulfonylureas. These drugs can be: long-acting sulfonamides, tubercolostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid and propanolol.

Sitagliptin

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

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

Metformin hydrochloride

***In Vivo* Assessment of Drug Interactions:** In healthy volunteers, the pharmacokinetics of propranolol and ibuprofen were not affected by metformin when co-administered in single-dose interaction studies. Metformin is negligibly bound to plasma proteins and is therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol and probenecid, as compared to sulfonylureas, which are extensively bound to serum protein.

9.3 Drug-Behavioural Interactions

Effects of Smoking, Alcohol, and Diet: The effects of smoking, diet, and alcohol use on the pharmacokinetics of sitagliptin and metformin hydrochloride modified-release tablets have not been specifically studied. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking APO-SITAGLIPTIN/METFORMIN XR, since alcohol intake potentiates the effect of metformin on lactate metabolism (see 2 CONTRAINDICATIONS). The risk of lactic acidosis is increased in acute alcohol intoxication, particularly in case of fasting or malnutrition or hepatic insufficiency. It is recommended that consumption of alcohol and alcohol-containing medicinal product be avoided.

9.4 Drug-Drug Interactions

Sitagliptin

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.

Metformin

Carbonic Anhydrase Inhibitors: Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with APO-SITAGLIPTIN/METFORMIN XR may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.

Glyburide: In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co- administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Drugs that reduce metformin clearance: Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis (see 7 WARNINGS AND PRECAUTIONS). In both single- and multiple-dose metformin-cimetidine drug interaction studies, there was a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Close monitoring of glycemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when such products are co-administered.

Levothyroxine: Levothyroxine can reduce the glucose-lowering effect of metformin.

Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated, changed, or stopped (see 7 WARNINGS AND PRECAUTIONS), and APO-SITAGLIPTIN/METFORMIN XR dosage adjusted as necessary.

Anticoagulant: Elimination rate of the anticoagulant phenprocoumon has been reported to be increased by 20% when used concurrently with metformin. Therefore, a close monitoring of the International Normalized Ratio (INR) is recommended in patients concurrently administering metformin and phenprocoumon or other antivitamin K anticoagulants (see 7 WARNINGS AND PRECAUTIONS). In such cases, an important increase of prothrombin time may occur upon cessation of APO-SITAGLIPTIN/METFORMIN XR therapy, with an increased risk of hemorrhage.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, isoniazid and beta-2-agonists. ACE-inhibitors may decrease the blood glucose levels. When such drugs are administered to a patient receiving APO-SITAGLIPTIN/METFORMIN XR the patient should be closely observed to maintain adequate glycemic control.

Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function.

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

Sitagliptin

Interactions with laboratory tests have not been established.

Metformin hydrochloride

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Sitagliptin and Metformin hydrochloride

APO-SITAGLIPTIN/METFORMIN XR combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class. APO-SITAGLIPTIN/METFORMIN XR targets three core defects of type 2 diabetes which are: decreased insulin synthesis and release, increased hepatic glucose production and decreased insulin sensitivity.

Sitagliptin

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 class of agents that act as incretin enhancer.

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.

Metformin hydrochloride

Metformin is a biguanide derivative producing an antihyperglycemic effect which can only be observed in man or in the diabetic animal and only when there is insulin secretion. Metformin, at therapeutic doses, does not cause hypoglycemia when used alone in man or in the non-diabetic animal, except when using a near lethal dose. Metformin has no effects on the pancreatic beta cells. The mode of action of metformin is not fully understood. It has been postulated that metformin might potentiate the effect of insulin or that it might enhance the effect of insulin on the peripheral receptor site. This increased sensitivity seems to follow an increase in the number of insulin receptors on cell surface membranes.

Metformin absorption is relatively slow and may extend over about 6 hours. Animal studies with metformin, labelled with 14C have shown that the drug is neither concentrated by liver cells nor is it excreted in the bile; it is concentrated in the intestinal mucosa and salivary glands.

It has been shown that, following a 2 g dose of metformin, the blood level remains

under 10 mcg/mL even at the peak, occurring 2 hours after absorption. During the experiments, metformin was shown to be devoid of any notable action in the body, apart from its specific metabolic activity.

In the healthy animal, metformin lowers blood sugar only at a nearly lethal dose. Different animal species are of unequal sensitivity. On the other hand, the animal with experimental diabetes, is sensitive to a much lower dosage, providing some insulin is still secreted.

The antihyperglycemic action of metformin is probably mediated through insulin:

Metformin improves the K co-efficient of glucose assimulation.

Metformin improves the co-efficient of insulin efficiency.

In the obese diabetic with hyperinsulinemia, metformin is reported to normalize insulin output. This normalizing effect is concurrent to that of glycemia.

Metformin has little effect on liver glycogen of the healthy animal. In low and average doses, no change occurs. In high doses nearing lethal levels, liver glycogen decreases. This lowering precedes the fall in blood sugar. This reaction represents a defense mechanism tending to mobilize body reserves in order to combat hypoglycemia.

In the diabetic animal with a low liver glycogen reserve, the opposite occurs and metformin builds up glycogen stores of the liver. *In vitro*, on muscular tissue isolated in Warburg's apparatus, metformin increases glucose uptake by the muscle. This action follows an aerobic pathway. Even in high concentration, contrary to phenethyl-biguanide, metformin apparently does not block respiration or change carbohydrate metabolism via the anaerobic pathway.

Metformin is eliminated in faeces and urine. It is rapidly excreted by the kidneys in an unchanged form.

Renal clearance is 450 mL/minute; this appears to explain the absence of accumulation.

Metabolites of metformin have not been identified, neither by radio-active nor by chemical methods.

A single Rf spot is always present following radiochromatographic study of urine and always corresponds to that of pure metformin. Administration during 10 consecutive days has not shown any sign of accumulation.

Inhibition of glyconeogenesis has been observed in animals following its stimulation by fasting, cortisol, alcohol or other substrates such as alanine lactate or pyruvate.

However, such an effect varies according to the type and dosage of the biguanide used, nutritional state of the animal species and design of experimental model.

This inhibition of glyconeogenesis is observed only in the presence of insulin and it does not appear to play an important role in man.

Inhibition of intestinal absorption of sugars, which is not related to a malabsorption phenomenon has been observed with biguanides under certain experimental conditions in animal and in man. In one study, a 20% retardation of galactose absorption was observed in man receiving metformin. However, such an effect of metformin could not be confirmed in another study in man.

Recent findings appear to indicate that most of the metabolic effects of the biguanides are exerted through a single mechanism, namely inhibition of fatty acid oxidation and of acetyl-CoA generation.

However, inhibition of insulin-stimulated lipogenesis which has also been observed appears to be due to the inhibition of acetyl-CoA carboxylase by the biguanides. Such an effect may explain, at least partly, the weight-reducing effect exerted by these drugs in obese diabetic patients.

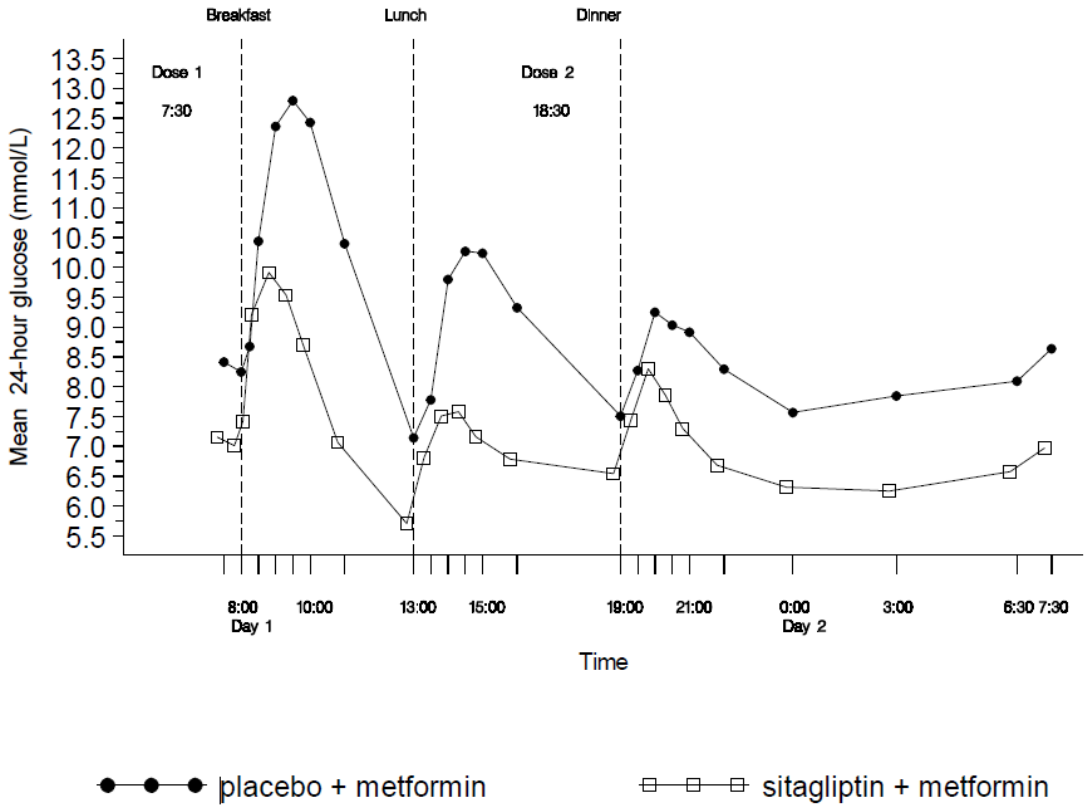
10.2 Pharmacodynamics

Sitagliptin

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, 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 11times 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.

Metformin hydrochloride

Few data are available on the relationship between pharmacodynamics and

pharmacokinetics, and therefore the effect of metformin on glucose control cannot be predicted from pharmacokinetic data alone. Tissue concentrations of metformin in the dual target sites of the liver and muscle appear to be more informative, and the deep metformin compartment supplying these tissues is critical and related to plasma concentrations. This view substantiates the clinical observation that the glucose-lowering action of metformin takes time to be fully expressed and also that activity is not lost immediately on drug withdrawal.

Sitagliptin and Metformin Co-Administration

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

10.3 Pharmacokinetics

The results of studies in healthy subjects demonstrated that the sitagliptin and metformin hydrochloride modified-release tablets 50 mg/500 mg and 100 mg/1000 mg combination tablets are bioequivalent to co-administration of corresponding individual doses of sitagliptin tablets and metformin hydrochloride modified-release tablets.

After administration of two sitagliptin and metformin hydrochloride modified-release tablets 50 mg/1000 mg tablets once daily with the evening meal for 7 days in healthy adult subjects, steady state for sitagliptin and metformin was reached by Day 4 and 5, respectively. The median T_{max} values for sitagliptin and metformin at steady state were approximately 3 and 8 hours post-dose, respectively.

Absorption:

Sitagliptin

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

Metformin hydrochloride

Metformin absorption is relatively slow and may extend over about 6 hours.

Following a single oral dose of 1000 mg metformin hydrochloride extended-release tablet once-daily after a meal, the time to reach maximum plasma metformin concentration (T_{max}) is approximately 7 to 8 hours. In both single and multiple dose studies in healthy subjects, once daily 1000 mg dosing provides equivalent systemic exposure, as measured by area-under-the-curve (AUC), of metformin relative to the immediate release given as 500 mg twice daily.

Once daily oral doses of metformin hydrochloride extended-release 500 mg to 2500

mg doses resulted in less than proportional increases in both AUC and C_{max}. The mean C_{max} values were 473 ± 145, 868 ± 223, 1171 ± 297, and 1630 ± 399 ng/mL for once daily doses of 500, 1000, 1500, and 2500 mg, respectively. For AUC, the mean values were 3501 ± 796, 6705 ± 1918, 9299 ± 2833, and 14161 ± 4432 ng.hr/mL for once daily doses of 500, 1000, 1500, and 2500 mg, respectively.

Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from 500 mg metformin hydrochloride extended-release tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected.

Distribution:

Sitagliptin

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

Metformin hydrochloride

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63 to 276 L.

Metabolism:

Sitagliptin

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.

Metformin hydrochloride

Metformin is not metabolized. Its main sites of concentration are the intestinal mucosa and the salivary glands. The plasma concentration at steady-state ranges about 1 to 2 mcg/mL. Certain drugs may potentiate the effects of metformin (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

Elimination:

Sitagliptin

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

urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

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

Metformin hydrochloride

The drug is excreted in urine at high renal clearance rate of about 450 mL/min. The initial elimination of metformin is rapid with a half-life varying between 1.7 and 3 hours. The terminal elimination phase accounting for about 4 to 5 % of the absorbed dose is slow with a half-life between 9 and 17 hours.

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:**

  Sitagliptin

  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.

  Metformin hydrochloride

  Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients.

  Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged and C_{max} is increased, compared to healthy

young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see 7 WARNINGS AND PRECAUTIONS, Special Populations).

- **Sex:**

  Sitagliptin

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

  Metformin hydrochloride

  In the pharmacokinetic studies in healthy volunteers, there were no important differences between male and female subjects with respect to metformin AUC (males = 268, females = 293) and $t_{½}$ (males = 229, females = 260). However, C_{max} for metformin were somewhat higher in female subjects (Female/Male C_{max} Ratio = 1.4). The gender differences for C_{max} are unlikely to be clinically important.

- **Ethnic Origin:**

  Sitagliptin

  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.

  Metformin hydrochloride

  In studies conducted with metformin extended-release, there were no definitive conclusions on the differences between the races with respect to the pharmacokinetics because of the imbalance in the respective sizes of the racial groups. However, the data suggest a trend towards higher metformin C_{max} and AUC values for metformin in Asian subjects when compared to Caucasian, Hispanic and Black subjects. The differences between the Asian and Caucasian groups are unlikely to be clinically important.

- **Hepatic Insufficiency:**

  APO-SITAGLIPTIN/METFORMIN XR is contraindicated in patients with severe hepatic impairment and should not be used in patients with clinical or laboratory evidence of hepatic disease (see 2 CONTRAINDICATIONS).

  Sitagliptin

  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.

Metformin hydrochloride

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

- **Renal Insufficiency:** APO-SITAGLIPTIN/METFORMIN XR is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) (see 2 CONTRAINDICATIONS).

Sitagliptin

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 insufficiency 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 eGFR <45 mL/min/1.73 m^2 (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

Metformin hydrochloride

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

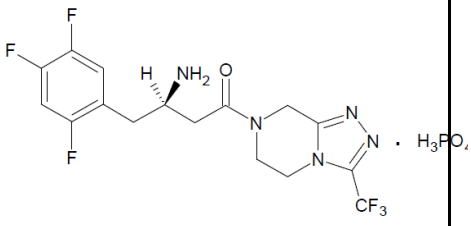
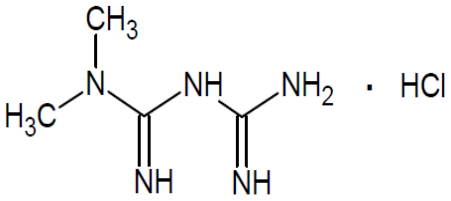
11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15ºC to 30ºC.

PART II : SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Sitagliptin phosphate monohydrate	Metformin hydrochloride
Chemical name:	7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4- triazolo[4,3-*a*]pyrazine phosphate (1 :1) monohydrate	Imidodicarbonimidic diamide, *N,N*-dimethyl- monohydrochloride 1,1-Dimethylbiguanide monohydrochloride
Molecular formula:	$C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$	$C_4H_{11}N_5 \cdot HCl$
Molecular mass:	523.32 g/mol	165.62 g/mol
Structural formula:		
Physicochemical properties:	Sitagliptin phosphate monohydrate is a white to off-white powder. It is soluble in water and *N,N*-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.	Metformin hydrochloride is a white or almost white powder. It is freely soluble in water slightly soluble in alcohol; practically insoluble in acetone, chloroform, ether and methylene chloride. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Clinical studies of the co-administration of sitagliptin and metformin demonstrated significant improvements in glycemic control in adult patients with type 2 diabetes. None of the clinical efficacy studies in adults described below were conducted with sitagliptin and metformin hydrochloride modified-release tablets; however, bioequivalence of sitagliptin and metformin hydrochloride modified-release tablets with co-administered sitagliptin and modified release metformin tablets has been demonstrated (see 10 CLINICAL PHARMACOLOGY).

Regimens of extended-release 500 mg metformin were at least as effective as corresponding regimens of an immediate-release 500 mg metformin in all measures of glycemic control. Additionally, once daily administration of two 500 mg extended-release metformin tablets was as effective as the commonly prescribed twice daily administration of the 500 mg immediate-release metformin formulation.

The combination of sitagliptin and metformin has been evaluated for safety and efficacy in four double-blind, placebo-controlled studies and in one double-blind, active controlled clinical study in patients with type 2 diabetes mellitus. In all studies, patients with inadequate glycemic control on stable doses of metformin ≥1500 mg were randomized to receive either sitagliptin 100 mg per day, or placebo or an active comparator, in addition to ongoing background therapy.

Sitagliptin in Combination with Metformin

Placebo-Controlled Study

Table 8 – Summary of Study Design and Patient Demographic

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.

In combination with metformin, sitagliptin provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo with metformin (Table 9). The improvement in HbA_{1c} was not affected by baseline HbA_{1c}, prior anti-hyperglycemic therapy, gender, age, 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). Body weight decreased from baseline in both treatment groups.

Table 9 – 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 ($p\geq0.05$) compared to placebo + metformin.

Active-Controlled (Sulfonylurea Agent) Study

Table 10 – Summary of Study Design and Patient Demographic

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P020	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 11 – Summary of Study Design and Patient Demographic

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	229	58.0 years (33–75)	Male: 120 Female: 109

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
		Metformin ≥1500 mg/day Oral 24-week			

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 12). 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 12 – 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
HbA_{1c} (%)	**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 HbA_{1c} <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 Metformin and Insulin

Table 13 – Summary of Study Design and Patient Demographic

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 + 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) 24-week	641	57.8 years (25–82)	Male: 326 Female: 315

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 100 mg once daily in combination with insulin.

Approximately 75% (n=462) of patients were also taking 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, and metformin (≥1500 mg per day) were randomized to the addition of either 100 mg of sitagliptin or placebo. 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}, FPG and 2-hour PPG.

The combination of sitagliptin, metformin and insulin provided significant improvements in HbA_{1c}, FPG and 2-hour PPG compared to placebo, metformin and insulin (Table 14). There was no meaningful change from baseline in body weight in either group.

Table 14 – Glycemic Parameters and Body Weight at Final Visit (24-Week Study) for Sitagliptin as Add-on Combination Therapy with Metformin and Insulin†

	Sitagliptin 100 mg + Insulin + Metformin	Placebo + Insulin + Metformin
HbA_{1c} (%)	**N=223**	**N=229**
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean‡)	-0.7	-0.1
Difference from placebo (adjusted mean‡, §)	-0.5*	
Patients (%) achieving HbA_{1c} <7%	32 (14.3)	12 (5.2)
FPG (mmol/L)	**N=225**	**N=229**
Baseline (mean)	9.6	9.8
Change from baseline (adjusted mean‡)	-1.2	-0.2
Difference from placebo (adjusted mean‡)	-1.0*	

	Sitagliptin 100 mg + Insulin + Metformin	Placebo + Insulin + Metformin
2-hour PPG (mmol/L)	**N=182**	**N=189**
Baseline (mean)	15.6	15.6
Change from baseline (adjusted mean‡)	-2.2	0.1
Difference from placebo (adjusted mean‡)	-2.2*	
Body Weight (kg)¶	**N=201**	**N=200**
Baseline (mean)	87.9	88.0
Change from baseline (adjusted mean‡)	-0.1	0.0
Difference from placebo (adjusted mean‡)	-0.1#	

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

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

§ Treatment by insulin stratum interaction was not significant (p>0.10).

* p<0.001 compared to placebo.

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

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

Add-on Combination Therapy with Metformin plus Pioglitazone

Table 15 – Summary of Patient Demographics for Clinical Trials in Specific Indication

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 16). Lipid effects were generally neutral. The difference between

sitagliptin and placebo in body weight change was not significant.

Table 16 – 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≥0.05) compared to placebo.

TECOS Cardiovascular Safety Study: The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a randomized, double-blind, placebo-controlled, parallel-group, event- driven, multicenter 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 patients (70.7% male, 29.3% female) 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 patients with type 2 diabetes. Superiority to placebo was not demonstrated for any endpoint (Table 17).

Table 17 – Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes Censored at 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						

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

Metformin hydrochloride

The prospective randomized (UKPDS) study has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- A significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), p=0.0023, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), p=0.0034.

- A significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, p=0.017. There was no significant difference between the metformin group and those assigned intensive therapy with sulfonylurea or insulin.

- A significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years (p=0.011), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p=0.021).

- A significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years (p=0.01). There was no significant difference between the metformin group and those assigned intensive therapy with sulfonylurea or insulin.

There were no significant differences between the metformin group and the diet alone in the other aggregate endpoints (stroke, peripheral vascular disease and microvascular complications).

14.2 Comparative Bioavailability Studies

A randomized, single-dose, two-way crossover comparative bioavailability study was conducted under fasting conditions in healthy male volunteers. Plasma sitagliptin and metformin concentrations were measured, and the rate and extent of absorption were compared following a single oral dose (1 x 50 mg/500 mg sitagliptin / metformin hydrochloride) of Apo-Sitagliptin/Metformin XR (Apotex Inc.) and Janumet® XR (Merck Canada Inc.) modified-release tablets. The results obtained from 27 volunteers who completed the study are summarized in the following tables.

Sitagliptin (1 x 50 mg/500 mg sitagliptin / metformin hydrochloride) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Mean	90% Confidence Interval (%)
AUC_t (ng•h/mL)	2022.75 2046.28 (15.3)	2013.88 2038.77 (15.9)	100.4	97.5-103.5
AUC_I (ng•h/mL)	2074.34 2097.78 (15.0)	2062.27 2087.18 (15.7)	100.6	97.6-103.6
C_{max} (ng/mL)	183.41 185.85 (17.8)	173.79 175.91 (16.4)	105.5	99.0-112.5
T_{max}# (h)	2.50 (0.5–5.5)	2.50 (1.0–7.0)		
$T_{1/2}$§ (h)	11.58 (15.3)	11.64 (18.4)		

* Apo-Sitagliptin/Metformin XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 50 mg/500 mg modified-release tablets (Apotex Inc.)
† Janumet® XR (sitagliptin, as sitagliptin phosphate monohydrate /metformin hydrochloride) 50 mg/500 mg modified-release tablets (Merck Canada Inc.) was purchased in Canada.

Sitagliptin (1 x 50 mg/500 mg sitagliptin / metformin hydrochloride) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Mean	90% Confidence Interval (%)
# Expressed as the median (range) only § Expressed as the arithmetic mean (CV%) only				

Metformin (1 x 50 mg/500 mg sitagliptin / metformin hydrochloride) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Mean	90% Confidence Interval (%)
AUC_t (ng•h/mL)	7468.8 7763.9 (27.4)	7261.6 7633.3 (33.1)	102.9	93.1-113.6
AUC_I (ng•h/mL)	7562.5 7853.1 (27.1)	7358.6 7721.2 (32.6)	102.8	93.2-113.4
C_{max} (ng/mL)	815.5 832.4 (19.6)	773.9 798.6 (25.0)	105.4	99.4-111.7
T_{max}# (h)	4.5 (3.0–7.03)	4.5 (3.5–9.0)		
$T_{1/2}$§ (h)	4.28 (25.6)	4.15 (15.4)		
* Apo-Sitagliptin/Metformin XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 50 mg/500 mg modified-release tablets (Apotex Inc.) † Janumet® XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 50 mg/500 mg modified-release tablets (Merck Canada Inc.) was purchased in Canada. # Expressed as the median (range) only § Expressed as the arithmetic means (CV%) only				

A randomized, single-dose, two-way crossover comparative bioavailability study was conducted under fed conditions in healthy male volunteers. Plasma sitagliptin and metformin concentrations were measured and the rate and extent of absorption were compared following a single oral dose (1 x 50 mg/500 mg sitagliptin / metformin hydrochloride) of Apo-Sitagliptin/Metformin XR (Apotex Inc.) and Janumet® XR (Merck Canada Inc.) modified-release tablets. The results obtained from the 31 volunteers who completed the study are summarized in the following tables.

Sitagliptin (1 x 50 mg/500 mg sitagliptin / metformin hydrochloride) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval (%)
AUC_t (ng•h/mL)	1857.05 1877.53 (14.3)	1859.28 1880.48 (14.7)	99.9	97.3 - 102.5
AUC_I (ng•h/mL)	1907.28 1928.67	1908.78 1930.18 (14.6)	99.9	97.4 - 102.5

Sitagliptin (1 x 50 mg/500 mg sitagliptin / metformin hydrochloride) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval (%)
	(14.5)			
C_{max} (ng/mL)	149.74 153.01 (21.1)	148.17 151.32 (20.4)	101.1	95.5 - 106.9
T_{max}# (h)	3.0 (1.0–6.0)	2.5 (1.5–6.0)		
$T_{1/2}$§ (h)	11.02 (23.1)	10.92 (18.1)		

* Apo-Sitagliptin/Metformin XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 50 mg/500 mg modified-release tablets (Apotex Inc.)
† Janumet® XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 50 mg/500 mg modified-release tablets (Merck Canada Inc.) was purchased in Canada.
# Expressed as the median (range) only
§ Expressed as the arithmetic mean (CV%) only

Metformin (1 x 50 mg/500 mg sitagliptin / metformin hydrochloride) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Mean	90% Confidence Interval (%)
AUC_t (ng•h/mL)	7761.5 7988.0 (22.4)	7526.5 7805.6 (24.8)	103.1	97.9 - 108.6
AUC_I (ng•h/mL)	7854.3 8080.3 (22.3)	7620.4 7894.8 (24.4)	103.1	97.9 - 108.5
C_{max} (ng/mL)	655.5 670.2 (19.4)	623.4 645.4 (24.1)	105.2	99.3 - 111.3
T_{max}# (h)	7.0 (3.5–11.0)	7.0 (5.0–10.0)		
$T_{1/2}$§(h)	4.53 (37.5)	4.49 (41.8)		

* Apo-Sitagliptin/Metformin XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 50 mg/500 mg modified-release tablets (Apotex Inc.)
† Janumet® XR (sitagliptin, as sitagliptin phosphate monohydrate/metformin hydrochloride) 50 mg/500 mg modified-release tablets (Merck Canada Inc.) was purchased in Canada.
# Expressed as the median (range) only
§ Expressed as the arithmetic mean (CV%) only

A randomized, single-dose, two-way crossover comparative bioavailability study was conducted under fasting conditions in healthy male volunteers. Plasma sitagliptin and metformin concentrations were measured and the rate and extent of absorption were compared following a single oral dose (1 x 100 mg/1000 mg sitagliptin / metformin hydrochloride) of Apo-Sitagliptin/Metformin XR (Apotex Inc.) and Janumet® XR (Merck Canada Inc.) modified-release tablets. The results obtained from 26 volunteers who completed the study are summarized in the following table.

Sitagliptin
(1 x 100 mg/1000 mg sitagliptin / metformin hydrochloride)
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval (%)
AUC_t (ng•h/mL)	4544.70 4592.92 (10.1)	4940.48 4966.15 (11.2)	92.0	89.9 - 94.1
AUC_I (ng•h/mL)	4612.82 4662.61 (10.3)	5006.16 5032.64 (11.4)	92.1	90.0 - 94.3
C_{max} (ng/mL)	430.73 446.60 (24.6)	484.21 496.30 (20.6)	89.0	82.0 - 96.5
T_{max}# (h)	3.0 ((0.5–6.0)	3.25 (0.5–5.0)		
$T_{1/2}$§ (h)	11.48 (11.5)	11.03 (10.8)		

* Apo-Sitagliptin/Metformin XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 100 mg/1000 mg modified-release tablets) (Apotex Inc.)
† Janumet® XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 100 mg/1000 mg modified-release tablets (Merck Canada Inc.) was purchased in Canada.
# Expressed as the median (range) only
§ Expressed as the arithmetic mean (CV%) only

Metformin
(1 x 100 mg/1000 mg sitagliptin / metformin hydrochloride)
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval (%)
AUC_t (ng•h/mL)	12478.3 12957.2 (27.5)	12789.4 13409.8 (26.7)	97.6	91.4 - 104.2
AUC_I (ng•h/mL)	12595.3 13073.4 (27.3)	12909.4 13529.8 (26.6)	97.6	91.3 - 104.2
C_{max} (ng/mL)	1167.3 1190.9 (19.7)	1194.7 1224.8 (19.7)	97.7	92.5 - 103.2
T_{max}# (h)	5.5 (3.0–9.0)	5.0 (4.0–10.0)		

Metformin (1 x 100 mg/1000 mg sitagliptin / metformin hydrochloride) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval (%)
$T_{1/2}$§ (h)	5.49 (58.9)	5.14 (42.8)		

* Apo-Sitagliptin/Metformin XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 100 mg/1000 mg modified-release tablets (Apotex Inc.)
† Janumet® XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 100 mg/1000 mg modified-release tablets (Merck Canada Inc.) was purchased in Canada.
# Expressed as the median (range) only
§ Expressed as the arithmetic mean (CV%) only

A randomized, single-dose, two-way crossover comparative bioavailability study was conducted under fed conditions in healthy male volunteers. Plasma sitagliptin and metformin concentrations were measured and the rate and extent of absorption were compared following a single oral dose (1 x 100 mg/1000 mg sitagliptin / metformin hydrochloride) of Apo-Sitagliptin/Metformin XR (Apotex Inc.) and Janumet® XR (Merck Canada Inc.) modified-release tablets. The results obtained from 27 volunteers who completed the study are summarized in the following table.

Sitagliptin (1 x 100 mg/1000 mg sitagliptin / metformin hydrochloride) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval (%)
AUC_t (ng•h/mL)	4420.37 4481.60 (13.9)	4661.22 4706.29 (12.8)	94.8	93.1 - 96.6
AUC_I (ng•h/mL)	4493.02 4556.84 (14.1)	4741.38 4787.02 (12.6)	94.8	93.1 - 96.5
C_{max} (ng/mL)	405.71 418.79 (23.4)	422.48 433.09 (22.1)	96.0	91.6 - 100.7
T_{max}# (h)	2.5 (0.75–6.0)	3.0 (1.5–5.0)		
$T_{1/2}$§ (h)	11.30 (14.0)	11.34 (16.3)		

* Apo-Sitagliptin/Metformin XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 100 mg/1000 mg modified-release tablets (Apotex Inc.)
† Janumet® XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 100 mg/1000 mg modified-release tablets (Merck Canada Inc.) was purchased in Canada.
# Expressed as the median (range) only
§ Expressed as arithmetic mean (CV%) only

Metformin (1 x 100 mg/1000 mg sitagliptin / metformin hydrochloride) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval (%)
AUC_t (ng•h/mL)	13879.4 14270.6 (21.7)	14936.7 15321.1 (21.9)	92.9	86.8 - 99.5
AUC_I (ng•h/mL)	14056.4 14433.8 (21.1)	15074.7 15446.2 (21.6)	93.2	87.2 - 99.7
C_{max} (ng/mL)	1215.5 1229.1 (14.6)	1185.1 1203.3 (17.9)	102.6	97.7 -107.6
T_{max}# (h)	8.0 (4.0–11.0)	8.0 (6.0–12.0)		
$T_{1/2}$§ (h)	6.72 (83.5)	5.74 (81.4)		

* Apo-Sitagliptin/Metformin XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 100 mg/1000 mg modified-release tablets (Apotex Inc.)
† Janumet® XR (sitagliptin, as sitagliptin phosphate monohydrate / metformin hydrochloride) 100 mg/1000 mg modified-release tablets (Merck Canada Inc.) was purchased in Canada.
# Expressed as the median (range) only
§ Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

No animal studies have been conducted with the combined products in sitagliptin and metformin hydrochloride modified-release tablets to evaluate carcinogenesis, mutagenesis, impairment of fertility or effects on reproduction. The following data are based on the findings in studies with sitagliptin and metformin individually and a 16 week toxicity study in dogs with the concomitant administration of sitagliptin and metformin.

General Toxicology:

Acute Toxicity

Sitagliptin

The approximate LD_{50} 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 LD_{50} 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

Sitagliptin and Metformin

Preclinical toxicokinetic and oral toxicity studies in dogs have been conducted with the combined products in sitagliptin and metformin hydrochloride tablets.

In a sixteen-week oral toxicity study, female dogs were administered 20 mg/kg/day of metformin, alone or in combination with 2, 10, or 50 mg/kg/day of sitagliptin. Transient ataxia and/or tremors were observed in the high-dose combination-treatment group. These signs were considered to be an effect of sitagliptin because they were seen in previous dog studies with sitagliptin alone at 50 mg/kg/day. The no-effect level for treatment-related changes in this study was 10 mg/kg/day of sitagliptin plus 20 mg/kg/day of metformin, which provided systemic exposure to sitagliptin of approximately 6 times that in patients treated with 100 mg/day of sitagliptin and systemic exposure to metformin of approximately 2.5 times that in patients treated with 2000 mg/day of metformin.

Sitagliptin

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:

Sitagliptin

A two-year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of 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).

Metformin hydrochloride

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

A carcinogenicity study was also conducted via dermal administration in Tg.AC transgenic mice at doses up to and including 2000 mg/kg/day. No evidence of carcinogenicity was observed in either male or female mice.

Genotoxicity:

Sitagliptin

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.

Metformin hydrochloride

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Reproductive and Developmental Toxicology:

No animal studies have been conducted with the combined products in sitagliptin and metformin hydrochloride modified-release tablets to evaluate effects on reproduction.

The following data are based on findings in studies performed with sitagliptin or metformin individually.

Sitagliptin

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.

Metformin hydrochloride

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

A decrease in male reproductive organ weights was observed at higher oral dose of 900 mg/kg/day in a fertility and developmental toxicity study in rats.

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

17 SUPPORTING PRODUCT MONOGRAPHS

1. JANUMET® XR (sitagliptin and metformin hydrochloride modified-release tablets 50 mg/500 mg, 50 mg/1000 mg and 100 mg/1000 mg), submission control 242894, Product Monograph, Merck Canada Inc. Date of Revision: July 27, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAPO-SITAGLIPTIN/METFORMIN XR

sitagliptin (as sitagliptin phosphate monohydrate) and metformin hydrochloride modified-release tablets

Read this carefully before you start taking **APO-SITAGLIPTIN/METFORMIN XR** 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 **APO-SITAGLIPTIN/METFORMIN XR**.

Serious Warnings and Precautions

- **Lactic acidosis** is a rare but serious buildup of acid in the blood. It can cause death. It must be treated in the hospital. APO-SITAGLIPTIN/METFORMIN XR contain the medicinal ingredient metformin hydrochloride. If you build up too much metformin in your blood you are at risk for lactic acidosis.

  Alcohol increases the risk of lactic acidosis caused by metformin. Do not "binge" drink or drink alcohol often when you are taking APO-SITAGLIPTIN/METFORMIN XR.

What is APO-SITAGLIPTIN/METFORMIN XR used for?

APO-SITAGLIPTIN/METFORMIN XR 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 are not controlled on metformin alone or currently on sitagliptin and metformin;
- in combination with a sulfonylurea, in patients who are not controlled on metformin and a sulfonylurea.
- in combination with premixed or long/intermediate acting insulin.
- in combination with pioglitazone, in patients who are not controlled on metformin and pioglitazone.

How does APO-SITAGLIPTIN/METFORMIN XR work?

APO-SITAGLIPTIN/METFORMIN XR contain the medicinal ingredients sitagliptin and metformin. These two medicines work together to help you achieve better blood sugar control.

Sitagliptin is a member of a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors). Sitagliptin helps to improve the levels of insulin when blood

sugar level is high, especially after a meal. Sitagliptin also helps to decrease the amount of sugar made by the body. Sitagliptin is unlikely to cause low blood sugar (**hypoglycemia**).

Metformin is a member of the biguanide class of medicines, it helps to lower the amount of sugar made by the liver.

What are the ingredients in APO-SITAGLIPTIN/METFORMIN XR?

- Medicinal ingredients: Sitagliptin phosphate monohydrate and metformin hydrochloride

- Non-medicinal ingredients: colloidal silicon dioxide, hypromellose, indigotine AL Lake 12-14%, magnesium stearate, methyl cellulose, polyethylene glycol, polyvinyl alcohol, propyl gallate, talc and titanium dioxide.

The APO-SITAGLIPTIN/METFORMIN XR 50 mg/1000 mg tablet contains the additional non-medicinal ingredient: yellow ferric oxide.

APO-SITAGLIPTIN/METFORMIN XR comes in the following dosage forms:

APO-SITAGLIPTIN/METFORMIN XR tablets contain immediate release sitagliptin (as sitagliptin phosphate monohydrate) /extended-release metformin hydrochloride 50 mg/500 mg, 50 mg/1000 mg or 100 mg/1000 mg.

Do not use APO-SITAGLIPTIN/METFORMIN XR if you:

- are allergic (hypersensitive) to sitagliptin, metformin, or any of the other ingredients in APO-SITAGLIPTIN/METFORMIN XR.
- have unstable and/or insulin-dependent (type 1) diabetes mellitus.
- have metabolic acidosis (including diabetic ketoacidosis, history or ketoacidosis or lactic acidosis – too much acid in the blood).
- have severe kidney disease.
- have liver problems.
- drink alcohol very often or drink a lot of alcohol in the short term ("binge" drinking).
- have severe heart problems or heart failure.
- have a lack of oxygen in the blood. This is called hypoxemia. This can happen when you have conditions that affect your heart or breathing.
- are stressed, have severe infections, are experiencing trauma, are about to have surgery, or are recovering from surgery.
- have severe **dehydration** (have lost a lot of water from your body) or shock.
- are breastfeeding.
- are pregnant or planning to become pregnant.
- are going to get or receive an injection of dye or contrast agent for an x-ray procedure. Talk to your healthcare professional about when to stop APO-SITAGLIPTIN/METFORMIN XR and when to start again.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-SITAGLIPTIN/METFORMIN XR. Talk about any health conditions or problems you may have, including if you:

- are older than 65 years of age;
- 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 heart problems including congestive heart failure (a condition where your heart becomes weaker and less able to pump the blood that your body needs);
- have or have had severe kidney problems;
- have liver problems;
- had an organ transplant;
- have human immunodeficiency syndrome (HIV);
- have vitamin B_{12} deficiency or anemia;
- have hypothyroidism (low levels of thyroid hormones).

Other warnings you should know about:

Lactic Acidosis (high levels of lactic acid in your blood):

- **You have a higher chance of getting lactic acidosis if you:**
  - have severe kidney problems;
  - have liver problems;
  - have congestive heart failure that requires treatment with medicines;
  - drink a lot of alcohol (very often or short-term "binge" drinking);
  - get **dehydration** (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and don't drink enough fluids. Tell your healthcare professional if this happens;
  - have certain x-ray tests with injectable dyes or contrast agents used. Tell your healthcare professional if you are going to have these types of tests. APO-SITAGLIPTIN/METFORMIN XR are usually stopped before the test and for two days after;
  - have surgery. Talk with your healthcare professional before any surgery if you must restrict what you eat and drink. In these cases, APO-SITAGLIPTIN/METFORMIN XR should be stopped for 2 days before the surgery. Wait until you are eating and drinking again before you restart APO-SITAGLIPTIN/METFORMIN XR;
  - have a heart attack, severe infection, or stroke;
  - take other medications.

Serious Skin Reactions and Pancreatitis:

- **APO-SITAGLIPTIN/METFORMIN XR 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 taking APO-SITAGLIPTIN/METFORMIN XR.

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 APO-SITAGLIPTIN/METFORMIN XR is used with a sulfonylurea medicine or with insulin, **hypoglycemia** (low blood sugar) can occur. Lower doses of the sulfonylurea medicine or insulin may be required while you take APO-SITAGLIPTIN/METFORMIN XR. You should use caution when driving or using machines if you are taking APO-SITAGLIPTIN/METFORMIN XR with a sulfonylurea medicine or with insulin.

Blood Tests:

- APO-SITAGLIPTIN/METFORMIN XR may cause abnormal blood tests. Your healthcare professional will do blood tests before you start APO-SITAGLIPTIN/METFORMIN XR and while you are taking it. They may check your blood sugar, liver and thyroid function, vitamin B_{12} levels 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.

If you start any new medicine, tell your healthcare professional.

The following may interact with APO-SITAGLIPTIN/METFORMIN XR:

- Other diabetes medicines such as glyburide.
- Furosemide, used to treat heart failure.
- Nifedipine, used to treat high blood pressure and chest pain.
- Ranolazine, used to treat chest pain.
- Vandetanib, used to treat thyroid cancer.
- Dolutegravir, used to treat HIV infection and AIDS.
- Cimetidine, used to treat stomach problems.
- Certain “blood thinners” used to prevent blood clots, such as phenprocoumon or other antivitamin K anticoagulants.
- Other medicines that tend to produce high blood sugar (hyperglycemia) and may lead to a loss of blood sugar control. Some examples include:

- Thiazide and other diuretics (water pills), used to treat high blood pressure
- Corticosteroids, used to treat joint pain and swelling
- Phenothiazines, used to treat schizophrenia
- Thyroid products
- Estrogens or estrogens plus progestogen
- Oral contraceptives (birth control pills)
- Phenytoin, used to treat epilepsy
- Nicotinic Acid, used to treat high cholesterol
- Sympathomimetics, used for heart problems
- Calcium channel blockers, used to treat high blood pressure
- Isoniazid, used to treat tuberculosis
- Beta-2-agonists, used to treat breathing problems
- Carbonic anhydrase inhibitors, used to treat glaucoma, heart failure, epilepsy and other conditions

- ACE inhibitors, used to treat high blood pressure, may lower blood glucose and the combination with APO-SITAGLIPTIN/METFORMIN XR should be carefully monitored.

How to take APO-SITAGLIPTIN/METFORMIN XR:

- Take APO-SITAGLIPTIN/METFORMIN XR exactly as your healthcare professional tells you to. Your healthcare professional will decide on the dose that is right for you based on the medicines you are currently taking. Do not stop taking APO-SITAGLIPTIN/METFORMIN XR or change your dose without taking to your healthcare professional.
- Your healthcare professional may change your dose based on your blood sugar levels.
- Take APO-SITAGLIPTIN/METFORMIN XR with food to avoid stomach upset.
- APO-SITAGLIPTIN/METFORMIN XR tablets are to be swallowed whole. Do **not** chew, cut, or crush the APO-SITAGLIPTIN/METFORMIN XR tablets.
- You may see something that looks like the APO-SITAGLIPTIN/METFORMIN XR tablet in your stool (bowel movement). If this happens, check your blood sugar. If your blood sugar control has changed, tell your healthcare professional.

Usual adult dose:

APO-SITAGLIPTIN/METFORMIN XR: Take your tablet(s) once a day preferably in the evening.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-SITAGLIPTIN/METFORMIN XR, 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 with food 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 two doses of APO-SITAGLIPTIN/METFORMIN XR at the same time to make up for a missed dose.

What are possible side effects from using APO-SITAGLIPTIN/METFORMIN XR?

These are not all the possible side effects that you may have when taking APO-SITAGLIPTIN/METFORMIN XR. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Stuffy or runny nose
- Sore throat
- Gastrointestinal symptoms: diarrhea, constipation, nausea, vomiting, abdominal bloating, upset stomach, gas and loss of appetite
- Headache
- Joint pain
- Arm or leg pain
- Back pain
- Muscle aches
- 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 a sulfonylurea or with insulin): shaking, sweating, rapid heartbeat, change in vision, hunger, headache and change in mood.		✓	
RARE			
Pancreatitis (inflammation of the pancreas): prolonged severe stomach pain and possible vomiting.			✓
Allergic reactions: rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.			✓
Serious skin reactions including Stevens-Johnson syndrome, bullous pemphigoid: blisters or breakdown of your skin.		✓	
Lactic acidosis (buildup of lactic acid in the blood): malaise or a feeling of general discomfort, uneasiness or pain;			

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**	
feeling very weak or tired; sleepiness, drowsiness or an increasing strong desire for sleep; low blood pressure, dizziness, lightheadedness; cold hands or feet; slow or irregular heartbeat, trouble breathing; unusual muscle pain; stomach pain with nausea, vomiting, or diarrhea.			✓
Encephalopathy (disease of the brain that severely alters thinking): muscle weakness in one area, poor decision-making or concentration, involuntary twitching, trembling, difficulty speaking or swallowing, seizures.			✓
Thyroid problems in patients with low thyroid function: fatigue, feeling cold, dry skin, poor memory and concentration, weight gain.		✓	
Acute kidney failure (sometimes requiring dialysis): nausea, loss of appetite and weakness, pass little or no urine, breathlessness.			✓
Hemolytic anemia (when red blood cells are destroyed faster than bone marrow can replace them): fatigue, pale color, rapid heartbeat, shortness of breath, dark urine, chills, and backache.			✓
Peripheral neuropathy (damage to the nerves in your arms or legs): gradual onset of numbness, prickling or tingling in your feet or hands, which can spread upward into your legs and arms, sharp, jabbing, throbbing, freezing or burning pain, extreme sensitivity to touch, lack of coordination and falling, muscle weakness or paralysis if motor nerves are affected.			✓
VERY RARE			
Vitamin B_{12} deficiency (decreased vitamin B_{12} levels in the blood): fatigue, shortness of breath, tingling or numbness of the fingers or toes, difficulty walking properly, irritability, confusion, tender calves.		✓	
Liver problems: yellow of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite.		✓	
Rhabdomyolysis (breakdown of damaged muscle): muscle spasms, weakness, red-brown (tea-coloured) urine.			✓

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:

Store at room temperature 15ºC to 30ºC.

Keep out of reach and sight of children.

If you want more information about APO-SITAGLIPTIN/METFORMIN XR:

- 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 manufacturer's website http://www.apotex.ca/products or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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