150092247
SAXAGLIPTIN AND METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SAXAGLIPTIN AND METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for SAXAGLIPTIN AND METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS.

SAXAGLIPTIN and METFORMIN HYDROCHLORIDE extended-release tablets, for oral use
Initial U.S. Approval: 2010

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

----------INDICATIONS AND USAGE ---------

Saxagliptin and metformin hydrochloride extended-release tablets are a combination of saxagliptin, a dipeptidyl peptidase-4 (DPP4) inhibitor, and metformin, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate. (1, 14)

Limitations of Use:
- Not used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1.1)

------ DOSAGE AND ADMINISTRATION------

- Administer once daily with the evening meal. (2.1)
- Individualize the starting dose based on the patient's current regimen then adjust the dosage based on effectiveness and tolerability. (2.1)
- Do not exceed a daily dosage of 5 mg saxagliptin/2,000 mg metformin HCl extended-release. (2.1)
- Swallow whole. Never crush, cut, or chew. (2.1)
- Limit the saxagliptin dosage to 2.5 mg daily for patients also taking strong cytochrome P450 3A4/5 inhibitors (e.g., ketoconazole). (2.2, 7.1)
- Assess renal function prior to initiation of saxagliptin and metformin hydrochloride extended-release tablets and periodically thereafter. (2.3)
  - ○ Do not use in patients with eGFR below 30 mL/min/1.73 m^2.
  - ○ Initiation is not recommended in patients with eGFR between 30 to 45 mL/min/1.73 m^2.
  - ○ Assess risk/benefit of continuing if eGFR falls below 45 mL/min/1.73 m^2.
  - ○ Limit the saxagliptin component to 2.5 mg daily if eGFR is less than 45 mL/min/1.73 m^2.
  - ○ Discontinue if eGFR falls below 30 mL/min/1.73 m^2.
- Saxagliptin and metformin hydrochloride extended-release tablets may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.4)

----- DOSAGE FORMS AND STRENGTHS ----

Tablets:
- 5 mg saxagliptin/500 mg metformin HCl extended-release (3)
- 5 mg saxagliptin/1,000 mg metformin HCl extended-release (3)
- 2.5 mg saxagliptin/1,000 mg metformin HCl extended-release (3)

------------CONTRAINDICATIONS -----------

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2). (4)
- Hypersensitivity to metformin hydrochloride. (4)
- Metabolic acidosis, including diabetic ketoacidosis. (4, 5.1)
- History of a serious hypersensitivity reaction (e.g., anaphylaxis, angioedema, exfoliative skin conditions) to saxagliptin and metformin hydrochloride extended-release tablets or saxagliptin. (4)

------ WARNINGS AND PRECAUTIONS ------

- *Lactic Acidosis:* See boxed warning. (5.1)
- *Pancreatitis:* If pancreatitis is suspected, promptly discontinue saxagliptin and metformin hydrochloride extended-release tablets. (5.2)
- *Heart Failure:* Consider the risks and benefits of saxagliptin and metformin hydrochloride extended-release tablets in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.3)
- *Vitamin B_{12} Deficiency:* Metformin may lower vitamin B_{12} levels. Measure hematological parameters annually. (5.4, 6.1)
- *Hypoglycemia:* In the saxagliptin add-on to sulfonylurea, add-on to insulin, and add-on to metformin plus sulfonylurea trials, confirmed hypoglycemia was reported more commonly in patients treated with saxagliptin compared to placebo. When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. (5.6, 6.1)
- *Hypersensitivity-Related Events (e.g., urticaria, facial edema):* More common in patients treated with saxagliptin than in patients treated with placebo; and post-marketing reports of serious hypersensitivity reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions in patients treated with saxagliptin. Promptly discontinue saxagliptin and metformin hydrochloride extended-release tablets, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.7, 6.1, 6.2)
- *Arthralgia:* Severe and disabling arthralgia has been reported in patients taking DPP4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.8)
- *Bullous Pemphigoid:* There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue saxagliptin and metformin hydrochloride extended-release tablets. (5.9)
- *Macrovascular Outcomes:* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with saxagliptin and metformin hydrochloride extended-release tablets. (5.10)

------------ ADVERSE REACTIONS -----------

- Adverse reactions reported in >5% of patients treated with metformin extended-release and more commonly than in patients treated with placebo are: diarrhea and nausea/vomiting. (6.1)
- Adverse reactions reported in ≥5% of patients treated with saxagliptin and more commonly than in patients treated with placebo are: upper respiratory tract infection, urinary tract infection, and headache. (6.1)
- Adverse reactions reported in ≥5% of treatment-naive patients treated with coadministered saxagliptin and metformin and more commonly than in patients treated with metformin alone are: headache and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dr. Reddy's Laboratories, Inc. at 1-888-375-3784 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

------------ DRUG INTERACTIONS -----------

- Coadministration with strong CYP3A4/5 inhibitors (e.g., ketoconazole) significantly increases saxagliptin concentrations. Limit saxagliptin and metformin hydrochloride extended-release tablets dose to 2.5 mg/1,000 mg once daily. (2.2, 7.1)
- Carbonic anhydrase inhibitors may increase the risk of lactic acidosis. Consider more frequent monitoring. (7.2)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7.3)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.4)

------ USE IN SPECIFIC POPULATIONS------

- *Geriatric Use:* Assess renal function more frequently. (8.5)
- *Hepatic Impairment*: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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FULL PRESCRIBING INFORMATION

> **WARNING: LACTIC ACIDOSIS**
> - **Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (> 5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL [*see Warnings and Precautions (5.1)*].**
> - **Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.**
> - **Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information [*see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)*].**
> - **If metformin-associated lactic acidosis is suspected, immediately discontinue saxagliptin and metformin hydrochloride extended-release tablets and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [*see Warnings and Precautions (5.1)*].**

1 INDICATIONS AND USAGE

Saxagliptin and metformin hydrochloride extended-release tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate [*see Clinical Studies (14)*].

1.1 Limitation of Use

Saxagliptin and metformin hydrochloride extended-release tablets are not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The dosage of saxagliptin and metformin hydrochloride extended-release tablets should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability. Saxagliptin and metformin hydrochloride extended-release tablets should generally be administered once daily with the evening meal, with gradual dose titration to reduce the gastrointestinal side effects associated with metformin. The following dosage forms are available:
- Saxagliptin and metformin hydrochloride extended-release tablets, 5 mg/500 mg
- Saxagliptin and metformin hydrochloride extended-release tablets, 5 mg/1,000 mg
- Saxagliptin and metformin hydrochloride extended-release tablets, 2.5 mg/1,000 mg

The recommended starting dose of saxagliptin and metformin hydrochloride extended-release tablets in patients who need 5 mg of saxagliptin and who are not currently treated with metformin is 5 mg saxagliptin/500 mg metformin extended-release once daily with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.

In patients treated with metformin, the dosage of saxagliptin and metformin hydrochloride extended-release tablets should provide metformin at the dose already being taken, or the nearest therapeutically appropriate dose. Following a switch from metformin immediate-release to metformin extended-release, glycemic control should be closely monitored and dosage adjustments made accordingly.

Patients who need 2.5 mg saxagliptin in combination with metformin extended-release may be treated with saxagliptin and metformin hydrochloride extended-release tablets 2.5 mg/1,000 mg. Patients who need 2.5 mg saxagliptin who are either metformin naive or who require a dose of metformin higher than 1,000 mg should use the individual components.

The maximum daily recommended dosage is 5 mg for saxagliptin and 2,000 mg for metformin extended-release.

No studies have been performed specifically examining the safety and efficacy of saxagliptin and metformin hydrochloride extended-release tablets in patients previously treated with other antihyperglycemic medications and switched to saxagliptin and metformin hydrochloride extended-release tablets. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

Inform patients that saxagliptin and metformin hydrochloride extended-release tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of saxagliptin and metformin hydrochloride extended-release tablets will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.

2.2 Dosage Adjustments with Concomitant Use of Strong CYP3A4/5 Inhibitors

The maximum recommended dosage of saxagliptin is 2.5 mg once daily when coadministered with strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). For these patients, limit the saxagliptin and metformin hydrochloride extended-release tablets dosage to 2.5 mg/1,000 mg once daily [*see Dosage and Administration (2.1), Drug Interactions (7.1),* and *Clinical Pharmacology (12.3)*].

2.3 Recommendations for Dosing and Administration in Renal Impairment

Assess renal function prior to initiation of saxagliptin and metformin hydrochloride extended-release tablets and periodically thereafter.

Saxagliptin and metformin hydrochloride extended-release tablets are contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.

Initiation of saxagliptin and metformin hydrochloride extended-release tablets in patients with an eGFR between 30 to 45 mL/minute/1.73 m^2 is not recommended.

In patients taking saxagliptin and metformin hydrochloride extended-release tablets whose eGFR later falls below 45 mL/minute/1.73 m^2, assess the benefit risk of continuing therapy and limit dose of the saxagliptin component to 2.5 mg once daily.

Discontinue saxagliptin and metformin hydrochloride extended-release tablets if the patient's eGFR later falls below 30 mL/minute/1.73 m^2 [*see Contraindications (4) and Warnings and Precautions (5.1)*].

2.4 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue saxagliptin and metformin hydrochloride extended-release tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; a history of liver disease, alcoholism or heart failure; or in any patient who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart saxagliptin and metformin hydrochloride extended-release tablets if renal function is stable [*see Warnings and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

- Saxagliptin and metformin hydrochloride extended-release tablets 5 mg/500 mg are light brown to brown colored, capsule shaped film-coated tablets imprinted with SM3 on one side and plain on other side and free from physical defects.
- Saxagliptin and metformin hydrochloride extended-release tablets 5 mg/1,000 mg are pink, colored, modified oval shaped film-coated tablets imprinted with SM2 on one side and plain on other side and free from physical defects.
- Saxagliptin and metformin hydrochloride extended-release tablets 2.5 mg/1,000 mg are pale yellow to light yellow colored, modified oval shaped film-coated tablets imprinted with SM1 on one side and plain on other side and free from physical defects.

4 CONTRAINDICATIONS

Saxagliptin and metformin hydrochloride extended-release tablets are contraindicated in patients with:
- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2).
- Hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to saxagliptin and metformin hydrochloride extended-release tablets or saxagliptin, such as anaphylaxis, angioedema, or exfoliative skin conditions [see *Warnings and Precautions (5.7)* and *Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis.

Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of saxagliptin and metformin hydrochloride extended-release tablets.

In saxagliptin and metformin hydrochloride extended-release tablets-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue saxagliptin and metformin hydrochloride extended-release tablets and report these symptoms to their healthcare provider.

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

Renal Impairment: The post-marketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include [*see Clinical Pharmacology (12.3)*].
- Before initiating saxagliptin and metformin hydrochloride extended-release tablets, obtain an estimated glomerular filtration rate (eGFR).
- Saxagliptin and metformin hydrochloride extended-release tablets are contraindicated in patients with an eGFR less than 30 mL/minute/1.73 m^2 [*see Contraindications (4)*].
- Initiation of saxagliptin and metformin hydrochloride extended-release tablets are not recommended in patients with eGFR between 30 and 45 mL/minute/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking saxagliptin and metformin hydrochloride extended-release tablets. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking saxagliptin and metformin hydrochloride extended-release tablets whose eGFR later falls below 45 mL/minute/1.73 m^2, assess the benefit and risk of continuing therapy.

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

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients [*see Use in Specific Populations (8.5)*].

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

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Saxagliptin and metformin hydrochloride extended-release tablets should be temporarily discontinued while patients have restricted food and fluid intake.

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

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving saxagliptin and metformin hydrochloride extended-release tablets.

Hepatic Impairment: Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of saxagliptin and metformin hydrochloride extended-release tablets in patients with clinical or laboratory evidence of hepatic disease.

5.2 Pancreatitis

There have been post-marketing reports of acute pancreatitis in patients taking saxagliptin. In a cardiovascular outcomes trial enrolling participants with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD (SAVOR trial), cases of definite acute pancreatitis were confirmed in 17 of 8,240 (0.2%) patients receiving saxagliptin compared to 9 of 8,173 (0.1%) receiving placebo. Pre-existing risk factors for pancreatitis were identified in 88% (15/17) of those patients receiving saxagliptin and in 100% (9/9) of those patients receiving placebo.

After initiation of saxagliptin and metformin hydrochloride extended-release tablets, observe patients for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue saxagliptin and metformin hydrochloride extended-release tablets and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using saxagliptin and metformin hydrochloride extended-release tablets.

5.3 Heart Failure

In a cardiovascular outcomes trial enrolling participants with established ASCVD or multiple risk factors for ASCVD (SAVOR trial), more patients randomized to saxagliptin (289/8,280, 3.5%) were hospitalized for heart failure compared to patients randomized to placebo (228/8,212, 2.8%). In a time-to-first-event analysis the risk of hospitalization for heart failure was higher in the saxagliptin group (estimated Hazard Ratio: 1.27; 95% CI: 1.07, 1.51). Subjects with a prior history of heart failure and subjects with renal impairment had a higher risk for hospitalization for heart failure, irrespective of treatment assignment.

Consider the risks and benefits of saxagliptin and metformin hydrochloride extended-release tablets prior to initiating treatment in patients at a higher risk for heart failure. Observe patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure, and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of saxagliptin and metformin hydrochloride extended-release tablets.

5.4 Vitamin B_{12} Concentrations

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on saxagliptin and metformin hydrochloride extended-release tablets and any apparent abnormalities should be appropriately investigated and managed [see *Adverse Reactions (6.1)*].

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful.

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

A patient with type 2 diabetes previously well controlled on saxagliptin and metformin hydrochloride extended-release tablets 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, saxagliptin and metformin hydrochloride extended-release tablets must be stopped immediately and other appropriate corrective measures initiated.

5.6 Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin

Saxagliptin

When saxagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of confirmed hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin [*see Adverse Reactions (6.1)*]. Therefore, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia when used in combination with saxagliptin and metformin hydrochloride extended-release tablets [*see Dosage and Administration (2.3)*].

Metformin hydrochloride

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

5.7 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with saxagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with saxagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue saxagliptin and metformin hydrochloride extended-release tablets, assess for other potential causes for the event, and institute alternative treatment for diabetes [*see Adverse Reactions (6.2)*].

Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with saxagliptin and metformin hydrochloride extended-release tablets.

5.8 Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP4 inhibitor. Consider DPP4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

5.9 Bullous Pemphigoid

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

5.10 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with saxagliptin and metformin hydrochloride extended-release tablets.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:
- Pancreatitis [*see Warnings and Precautions (5.2)*]
- Heart Failure [*see Warnings and Precautions (5.3)*]
- Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin [*see Warnings and Precautions (5.6)*]
- Hypersensitivity Reactions [*see Warnings and Precautions (5.7)*]
- Severe and disabling arthralgia [*see Warnings and Precautions (5.8)*]
- Bullous pemphigoid [*see Warnings and Precautions (5.9)*]

6.1 Clinical Trials Experience

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

Adverse Reactions in Efficacy Trials

Metformin hydrochloride

In placebo-controlled monotherapy trials of metformin extended-release, diarrhea and nausea/vomiting were reported in >5% of metformin-treated patients and more commonly than in placebo-treated patients (9.6% versus 2.6% for diarrhea and 6.5% versus 1.5% for nausea/vomiting). Diarrhea led to discontinuation of study medication in 0.6% of the patients treated with metformin extended-release.

Saxagliptin

The data in Table 1 are derived from a pool of 5 placebo-controlled clinical trials [*see Clinical Studies (14)*]. These data shown in the table reflect exposure of 882 patients to saxagliptin and a mean duration of exposure to saxagliptin of 21 weeks. The mean age of these patients was 55 years, 1.4% were 75 years or older and 48.4% were male. The population was 67.5% White, 4.6% Black or African American, 17.4% Asian, Other 10.5% and 9.8% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 5.2 years and a mean HbA1c of 8.2%. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60 mL/min/1.73 m^2) in 91% of these patients.

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of saxagliptin. These adverse reactions occurred more commonly on saxagliptin than on placebo and occurred in at least 5% of patients treated with saxagliptin.

Table 1: Adverse Reactions in Placebo-Controlled Trials* Reported in ≥5% of Patients Treated with Saxagliptin 5 mg and More Commonly than in Patients Treated with Placebo

	% of Patients	
	Saxagliptin 5 mg N=882	**Placebo N=799**
Upper respiratory tract infection	7.7	7.6
Urinary tract infection	6.8	6.1
Headache	6.5	5.9

* The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

In patients treated with saxagliptin 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate ≥5% and more commonly than in patients treated with placebo.

In the add-on to TZD trial, the incidence of peripheral edema was higher for saxagliptin 5 mg versus placebo (8.1% and 4.3%, respectively). The incidence of peripheral edema for saxagliptin 2.5 mg was 3.1%. None of the reported adverse reactions of peripheral edema resulted in study drug discontinuation. Rates of peripheral edema for saxagliptin 2.5 mg and saxagliptin 5 mg versus placebo were 3.6% and 2% versus 3% given as monotherapy, 2.1% and 2.1% versus 2.2% given as add-on therapy to metformin, and 2.4% and 1.2% versus 2.2% given as add-on therapy to glyburide.

The incidence rate of fractures was 1 and 0.6 per 100 patient-years, respectively, for saxagliptin (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The 10 mg saxagliptin dosage is not an approved dosage. The incidence rate of fracture events in patients who received saxagliptin did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of saxagliptin on bone.

An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to saxagliptin is not known.

Discontinuation of therapy due to adverse reactions occurred in 2.2%, 3.3%, and 1.8% of subjects receiving saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo, respectively. The most common adverse reactions (reported in at least 2 subjects treated with saxagliptin 2.5 mg or at least 2 subjects treated with saxagliptin 5 mg) associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%).

Adverse Reactions with Concomitant Use with Insulin

In the add-on to insulin trial [see *Clinical Studies (14.1)*], the incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between saxagliptin and placebo, except for confirmed hypoglycemia [see *Adverse Reactions (6.1)*].

Adverse Reactions Associated with Saxagliptin Coadministered with Metformin Immediate-Release in Treatment-Naive Patients with Type 2 Diabetes

Table 2 shows the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients participating in an additional 24-week, active-controlled trial of coadministered saxagliptin and metformin in treatment-naive patients.

Table 2: Coadministration of Saxagliptin and Metformin Immediate-Release in Treatment-Naive Patients: Adverse Reactions Reported in ≥5% of Patients Treated with Combination Therapy of Saxagliptin 5 mg Plus Metformin Immediate-Release (and More Commonly than in Patients Treated with Metformin Immediate-Release Alone)

	Number (%) of Patients	
	Saxagliptin 5 mg + Metformin* N=320	**Placebo + Metformin* N=328**
Headache	24 (7.5)	17 (5.2)
Nasopharyngitis	22 (6.9)	13 (4.0)

* Metformin immediate-release was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2,000 mg daily.

In patients treated with the combination of saxagliptin and metformin immediate-release, either as saxagliptin add-on to metformin immediate-release therapy or as coadministration in treatment-naive patients, diarrhea was the only gastrointestinal-related event that occurred with an incidence ≥5% in any treatment group in both studies. In the saxagliptin add-on to metformin immediate-release trial, the incidence of diarrhea was 9.9%, 5.8%, and 11.2% in the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. When saxagliptin and metformin immediate-release were coadministered in treatment-naive patients, the incidence of diarrhea was 6.9% in the saxagliptin 5 mg + metformin immediate-release group and 7.3% in the placebo + metformin immediate-release group.

Hypoglycemia

In the saxagliptin clinical trials, adverse reactions of hypoglycemia were based on all reports of hypoglycemia. A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflect true hypoglycemia.

The incidence of reported hypoglycemia for saxagliptin 2.5 mg and saxagliptin 5 mg versus placebo given as monotherapy was 4% and 5.6% versus 4.1%, respectively. In the add-on to metformin immediate-release trial, the incidence of reported hypoglycemia was 7.8% with saxagliptin 2.5 mg, 5.8% with saxagliptin 5 mg, and 5% with placebo. When saxagliptin and metformin immediate-release were coadministered in treatment-naive patients, the incidence of reported hypoglycemia was 3.4% in patients given saxagliptin 5 mg + metformin immediate-release and 4% in patients given placebo + metformin immediate-release.

In the active-controlled trial comparing add-on therapy with saxagliptin 5 mg to glipizide in patients inadequately controlled on metformin alone, the incidence of reported hypoglycemia was 3% (19 events in 13 patients) with saxagliptin 5 mg versus 36.3% (750 events in 156 patients) with glipizide. Confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤50 mg/dL) was reported in none of the saxagliptin-treated patients and in 35 glipizide-treated patients (8.1%) (p<0.0001).

In the saxagliptin add-on to insulin trial, the overall incidence of reported hypoglycemia was 18.4% for saxagliptin 5 mg and 19.9% for placebo. However, the incidence of confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤50 mg/dL) was higher with saxagliptin 5 mg (5.3%) versus placebo (3.3%). Among the patients using insulin in combination with metformin, the incidence of confirmed symptomatic hypoglycemia was 4.8% with saxagliptin versus 1.9% with placebo.

In the saxagliptin add-on to metformin plus sulfonylurea trial, the overall incidence of reported hypoglycemia was 10.1% for saxagliptin 5 mg and 6.3% for placebo. Confirmed hypoglycemia was reported in 1.6% of the saxagliptin-treated patients and in none of the placebo-treated patients [see *Warnings and Precautions (5.6)*].

Hypersensitivity Reactions

Saxagliptin

Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo, respectively. None of these events in patients who received saxagliptin required hospitalization or were reported as life-threatening by the investigators. One saxagliptin-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Renal Impairment

In the SAVOR trial, adverse reactions related to renal impairment, including laboratory changes (i.e., doubling of serum creatinine compared with baseline and serum creatinine >6 mg/dL), were reported in 5.8% (483/8,280) of saxagliptin-treated subjects and 5.1% (422/8,212) of placebo-treated subjects. The most frequently reported adverse reactions included renal impairment (2.1% vs. 1.9%), acute renal failure (1.4% vs. 1.2%), and renal failure (0.8% vs. 0.9%), in the saxagliptin versus placebo groups, respectively. From baseline to the end of treatment, there was a mean decrease in eGFR of 2.5 mL/min/1.73m^2 for saxagliptin-treated patients and a mean decrease of 2.4 mL/min/1.73m^2 for placebo-treated patients. More subjects randomized to saxagliptin (421/5,227, 8.1%) compared to subjects randomized to placebo (344/5,073, 6.8%) had downward shifts in eGFR from >50 mL/min/1.73 m^2 (i.e., normal or mild renal impairment) to ≤50 mL/min/1.73 m^2 (i.e., moderate or severe renal impairment). The proportions of subjects with renal adverse reactions increased with worsening baseline renal function and increased age, regardless of treatment assignment.

Infections

Saxagliptin

In the unblinded, controlled, clinical trial database for saxagliptin to date, there have been 6 (0.12%) reports of tuberculosis among the 4,959 saxagliptin-treated patients (1.1 per 1,000 patient-years) compared to no reports of tuberculosis among the 2,868 comparator-treated patients. Two of these six cases were confirmed with laboratory testing. The remaining cases had limited information or had presumptive diagnoses of tuberculosis. None of the six cases occurred in the United States or in Western Europe. One case occurred in Canada in a patient originally from Indonesia who had recently visited Indonesia. The duration of treatment with saxagliptin until report of tuberculosis ranged from 144 to 929 days. Post-treatment lymphocyte counts were consistently within the reference range for four cases. One patient had lymphopenia prior to initiation of saxagliptin that remained stable throughout saxagliptin treatment. The final patient had an isolated lymphocyte count below normal approximately four months prior to the report of tuberculosis. There have been no spontaneous reports of tuberculosis associated with saxagliptin use. Causality has not been established and there are too few cases to date to determine whether tuberculosis is related to saxagliptin use.

There has been one case of a potential opportunistic infection in the unblinded, controlled clinical trial database to date in a saxagliptin-treated patient who developed suspected foodborne fatal salmonella sepsis after approximately 600 days of saxagliptin therapy. There have been no spontaneous reports of opportunistic infections associated with saxagliptin use.

Vital Signs

Saxagliptin

No clinically meaningful changes in vital signs have been observed in patients treated with saxagliptin alone or in combination with metformin.

Laboratory Tests

Absolute Lymphocyte Counts

Saxagliptin

There was a dose-related mean decrease in absolute lymphocyte count observed with saxagliptin. From a baseline mean absolute lymphocyte count of approximately 2,200 cells/microL, mean decreases of approximately 100 and 120 cells/microL with saxagliptin 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when saxagliptin 5 mg and metformin were coadministered in treatment-naive patients compared to placebo and metformin. There was no difference observed for saxagliptin 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 0.5%, 1.5%, 1.4%, and 0.4% in the saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to saxagliptin although some patients had recurrent decreases upon rechallenge that led to discontinuation of saxagliptin. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The 10 mg saxagliptin dosage is not an approved dosage.

In the SAVOR trial mean decreases of approximately 84 cells/microL with saxagliptin relative to placebo was observed. The proportion of patients who experienced a decrease in lymphocyte counts to a count of ≤750 cells/microL was 1.6% (136/8,280) and 1% (78/8,212) on saxagliptin and placebo respectively.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of saxagliptin on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

Vitamin B_{12} Concentrations

Metformin hydrochloride

Metformin may lower serum vitamin B_{12} concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on saxagliptin and metformin hydrochloride extended-release tablets and any apparent abnormalities should be appropriately investigated and managed [see *Warnings and Precautions (5.4)*].

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use. 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.

Saxagliptin
- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions
- Pancreatitis
- Severe and disabling arthralgia
- Bullous pemphigoid
- Rhabdomyolysis

Metformin hydrochloride
- Cholestatic, hepatocellular, and mixed hepatocellular liver injury

7 DRUG INTERACTIONS

7.1 Strong Inhibitors of CYP3A4/5 Enzymes

Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of saxagliptin should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor [*see Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

7.2 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with saxagliptin and metformin hydrochloride extended-release tablets may increase the risk for lactic acidosis.

7.3 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 Clinical Pharmacology (12.3)*]. Consider the benefits and risks of concomitant use.

7.4 Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving saxagliptin and metformin hydrochloride extended-release tablets.

7.5 Insulin Secretagogues or Insulin

In the saxagliptin add-on to sulfonylurea, add-on to insulin, and add-on to metformin plus sulfonylurea trials, confirmed hypoglycemia was reported more commonly in patients treated with saxagliptin compared to placebo. When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia.

7.6 Use with Other Drugs

Some medications can predispose to hyperglycemia and may lead to loss of glycemic control. These medications include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving saxagliptin and metformin hydrochloride extended-release tablets, the patient should be closely observed for loss of glycemic control. When such drugs are withdrawn from a patient receiving saxagliptin and metformin hydrochloride extended-release tablets, the patient should be observed closely for hypoglycemia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with saxagliptin and metformin hydrochloride extended-release tablets or saxagliptin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk [*see Data*].

No adverse developmental effects independent of maternal toxicity were observed when saxagliptin and metformin were administered separately or in combination to pregnant rats and rabbits during the period of organogenesis [*see Data*].

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with an HbA1c greater than 7 and has been reported to be as high as 20 to 25% in women with an HbA1c greater than 10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Data

Animal Data

Saxagliptin

In embryo-fetal development studies, saxagliptin was administered to pregnant rats and rabbits during the period of organogenesis, corresponding to the first trimester of human pregnancy. No adverse developmental effects were observed in either species at exposures 1,503- and 152-times the 5 mg clinical dose in rats and rabbits, respectively, based on AUC. Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

In a prenatal and postnatal development study, no adverse developmental effects were observed in maternal rats administered saxagliptin from gestation day 6 through lactation day 21 at exposures up to 470-times the 5 mg clinical dose, based on AUC.

Metformin hydrochloride

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

Saxagliptin and Metformin

Saxagliptin and metformin coadministered to pregnant rats and rabbits during the period of organogenesis did not result in adverse developmental effects considered relevant in either species. Doses tested in rats provided exposure up to 100- and 10-times clinical exposure, and doses tested in rabbits provided exposure up to 249- and 1-times clinical exposure relative to the clinical dose of 5 mg saxagliptin and 2,000 mg metformin. Minor skeletal abnormalities associated with maternal toxicity were observed in rats. In rabbits, coadministration was poorly tolerated in a subset of mothers (12 of 30), resulting in death, moribundity, or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29, associated with fetal body weight decrements of 7%, and a low incidence of delayed ossification of the fetal hyoid bone.

8.2 Lactation

Risk Summary

There is no information regarding the presence of saxagliptin and metformin hydrochloride extended-release tablets or saxagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk [*see Data*]. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Saxagliptin is present in the milk of lactating rats [*see Data*].

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for saxagliptin and metformin hydrochloride extended-release tablets and any potential adverse effects on the breastfed child from saxagliptin and metformin hydrochloride extended-release tablets or from the underlying maternal condition.

Data

Human

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

Animals

No studies is lactating animals have been conducted with the combined components of saxagliptin and metformin hydrochloride extended-release tablets. In studies performed with the individual components, both saxagliptin and metformin are secreted in the milk of lactating rats. Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations.

8.4 Pediatric Use

Safety and effectiveness of saxagliptin and metformin hydrochloride extended-release tablets in pediatric patients under 18 years of age have not been established. Additionally, studies characterizing the pharmacokinetics of saxagliptin and metformin hydrochloride extended-release tablets in pediatric patients have not been performed.

8.5 Geriatric Use

Saxagliptin and metformin hydrochloride extended-release tablets

Elderly patients are more likely to have decreased renal function. Assess renal function more frequently in the elderly [*see Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

Saxagliptin

In the seven, double-blind, controlled clinical safety and efficacy trials of saxagliptin, a total of 4,751 (42%) of the 11,301 patients randomized to saxagliptin were 65 years and over, and 1,210 (10.7%) were 75 years and over. No overall differences in safety or effectiveness were observed between subjects ≥65 years old and younger subjects. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients [*see Contraindications (4), Warnings and Precautions (5.1),* and *Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Saxagliptin

In a 12-week randomized placebo-controlled trial, saxagliptin 2.5 mg was administered to 85 subjects with moderate (n=48) or severe (n=18) renal impairment or end-stage renal disease (ESRD) (n=19) [*see Clinical Studies (14)*]. The incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between saxagliptin and placebo. The overall incidence of reported hypoglycemia was 20% among subjects treated with saxagliptin 2.5 mg and 22% among subjects treated with placebo. Four saxagliptin-treated subjects (4.7%) and three placebo-treated subjects (3.5%) reported at least one episode of confirmed symptomatic hypoglycemia (accompanying fingerstick glucose ≤50 mg/dL).

Metformin hydrochloride

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Saxagliptin and metformin hydrochloride extended-release tablets are contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 [*see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Saxagliptin and metformin hydrochloride extended-release tablets are not recommended in patients with hepatic impairment [*see Warnings and Precautions (5.1)*].

10 OVERDOSAGE

Saxagliptin

In a controlled clinical trial, once-daily, orally administered saxagliptin in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

Metformin hydrochloride

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

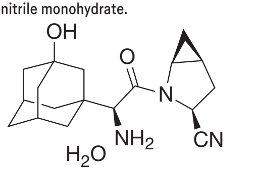
11 DESCRIPTION

Saxagliptin and metformin hydrochloride extended-release tablets contain two oral antihyperglycemic medications used in the management of type 2 diabetes: saxagliptin and metformin hydrochloride.

Saxagliptin

Saxagliptin is an orally active inhibitor of the dipeptidyl-peptidase-4 (DPP4) enzyme.

Saxagliptin monohydrate is described chemically as (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl) acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile monohydrate or (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxyadamantan-1-yl) acetyl]-2-azabicyclo [3.1.0]hexane-3-carbonitrile monohydrate.

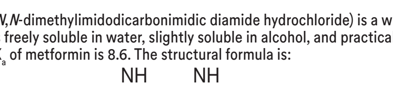


$C_{18}H_{25}N_3O_2 \bullet H_2O$ M.W. 333.43

Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic powder. It is very soluble at room temperate in methanol, freely soluble in ethanol, soluble in acetone, sparingly soluble in ethyl acetate and water, and slightly soluble in 1-octanol.

Metformin hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is a white crystalline powder. Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol, and practically insoluble in acetone and in methylene chloride. The pK_a of metformin is 8.6. The structural formula is:



$C_4H_{11}N_5 \bullet HCl$ M.W. 165.62

Saxagliptin and metformin hydrochloride extended-release tablets

Saxagliptin and metformin hydrochloride extended-release tablets are available for oral administration as tablets containing either 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and 500 mg metformin hydrochloride USP (saxagliptin and metformin hydrochloride extended-release tablets 5 mg/500 mg), or 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and 1,000 mg metformin hydrochloride USP (saxagliptin and metformin hydrochloride extended-release tablets 5 mg/1,000 mg), or 2.79 saxagliptin hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin and 1,000 mg metformin hydrochloride USP (saxagliptin and metformin hydrochloride extended-release tablets 2.5 mg/1,000 mg).

Each film-coated tablet of saxagliptin and metformin hydrochloride extended-release tablets contains the following inactive ingredients: colloidal silicon dioxide, hydrochloric acid, hypromellose, iron oxide black, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, propylene glycol, shellac, talc, titanium dioxide. In addition, 5 mg/500 mg tablets contain iron oxide red and iron oxide yellow; 5 mg/1,000 mg tablets contain iron oxide red; 2.5 mg/1,000 mg tablets contain iron oxide yellow.

The biologically inert components of the tablet may occasionally remain intact during gastrointestinal transit and will be eliminated in the feces as a soft, hydrated mass.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Saxagliptin and metformin hydrochloride extended-release tablets

Saxagliptin and metformin hydrochloride extended-release tablets combine two antihyperglycemic medications with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes: saxagliptin, a dipeptidyl-peptidase-4 (DPP4) inhibitor, and metformin hydrochloride, a biguanide.

Saxagliptin

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the DPP4 enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Saxagliptin is a competitive DPP4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus.

Metformin hydrochloride

Metformin improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in patients with type 2 diabetes or in healthy subjects except in unusual circumstances [*see Warnings and Precautions (5.6)*] and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

12.2 Pharmacodynamics

Saxagliptin

In patients with type 2 diabetes mellitus, administration of saxagliptin inhibits DPP4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent insulin secretion from pancreatic beta cells. The rise in insulin and decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Cardiac Electrophysiology

Saxagliptin

In a randomized, double-blind, placebo-controlled, 4-way crossover, active comparator study using moxifloxacin in 40 healthy subjects, saxagliptin was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 40 mg (8 times the MRHD).

12.3 Pharmacokinetics

Saxagliptin and metformin hydrochloride extended-release tablets

Bioequivalence and food effect of saxagliptin and metformin hydrochloride extended-release tablets was characterized under low calorie diet. The low calorie diet consisted of 324 kcal with meal composition that contained 11.1% protein, 10.5% fat, and 78.4% carbohydrate. The results of bioequivalence studies in healthy subjects demonstrated that saxagliptin and metformin hydrochloride extended-release combination tablets are bioequivalent to coadministration of corresponding doses of saxagliptin (ONGLYZA®) and metformin hydrochloride extended-release (GLUCOPHAGE® XR) as individual tablets under fed conditions.

Saxagliptin

The pharmacokinetics of saxagliptin and its active metabolite, 5-hydroxy saxagliptin were similar in healthy subjects and in patients with type 2 diabetes mellitus. The C_{max} and AUC values of saxagliptin and its active metabolite increased proportionally in the 2.5 to 400 mg dose range. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its active metabolite were 78 ng•h/mL and 214 ng•h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The average variability (%CV) for AUC and C_{max} for both saxagliptin and its active metabolite was less than 25%.

No appreciable accumulation of either saxagliptin or its active metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence were observed in the clearance of saxagliptin and its active metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 to 400 mg.

Metformin hydrochloride extended-release

Metformin extended-release C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. At steady state, the AUC and C_{max} are less than dose proportional for metformin extended-release within the range of 500 to 2,000 mg. After repeated administration of metformin extended-release, metformin did not accumulate in plasma. Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism. Peak plasma levels of metformin extended-release tablets are approximately 20% lower compared to the same dose of metformin immediate-release tablets, however, the extent of absorption (as measured by AUC) is similar between extended-release tablets and immediate-release tablets.

Absorption

Saxagliptin

The median time to maximum concentration (T_{max}) following the 5 mg once daily dose was 2 hours for saxagliptin and 4 hours for its active metabolite. Administration with a high-fat meal resulted in an increase in T_{max} of saxagliptin by approximately 20 minutes as compared to fasted conditions. There was a 27% increase in the AUC of saxagliptin when given with a meal as compared to fasted conditions. Food has no significant effect on the pharmacokinetics of saxagliptin when administered as saxagliptin and metformin hydrochloride extended-release combination tablets.

Metformin hydrochloride

Following a single oral dose of metformin extended-release, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. Although the extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin extended-release. Food has no significant effect on the pharmacokinetics of metformin when administered as saxagliptin and metformin hydrochloride extended-release combination tablets.

Distribution

Saxagliptin

The *in vitro* protein binding of saxagliptin and its active metabolite in human serum is negligible. Therefore, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

Metformin hydrochloride

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. 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 the sulfonylureas, which are extensively bound to serum proteins.

Metabolism

Saxagliptin

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a DPP4 inhibitor, which is one-half as potent as saxagliptin. Therefore, strong CYP3A4/5 inhibitors and inducers will alter the pharmacokinetics of saxagliptin and its active metabolite [*see Drug Interactions (7.1)*].

Metformin hydrochloride

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Metabolism studies with extended-release metformin tablets have not been conducted.

Excretion

Saxagliptin

Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its active metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion. A total of 22% of the administered radioactivity was recovered in feces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract. Following a single oral dose of saxagliptin 5 mg to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.

Metformin hydrochloride

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

Specific Populations

Renal Impairment

Saxagliptin

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function. The 10 mg dosage is not an approved dosage. The degree of renal impairment did not affect C_{max} of saxagliptin or its metabolite. In subjects with moderate renal impairment with eGFR 30 to less than 45 mL/min/1.73 m^2, severe renal impairment (eGFR 15 to less than 30 mL/min/1.73 m^2) and ESRD patient on hemodialysis, the AUC values of saxagliptin or its active metabolite were >2 fold higher than AUC values in subjects with normal renal function.

Metformin hydrochloride

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

Hepatic Impairment

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

MEDICATION GUIDE

Saxagliptin and Metformin Hydrochloride
(sax-a-GLIP-tin and met-FOR-min hye-droe-KLOR-ide)
Extended-Release Tablets, for oral use

What is the most important information I should know about saxagliptin and metformin hydrochloride extended-release tablets?

Serious side effects can happen in people taking saxagliptin and metformin hydrochloride extended-release tablets, including:

1. Lactic acidosis. Metformin, one of the medicines in saxagliptin and metformin hydrochloride extended-release tablets, can cause a rare but serious condition called lactic acidosis (a build-up of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:
- you feel cold in your hands or feet
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you feel sleepy or drowsy
- you have stomach pains, nausea or vomiting

Most people who have had lactic acidosis with metformin have other things that, combined with the metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with saxagliptin and metformin hydrochloride extended-release tablets if you:
- have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye
- have liver problems
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids
- have surgery
- have a heart attack, severe infection, or stroke

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your saxagliptin and metformin hydrochloride extended-release tablets for a while if you have any of these things.

Saxagliptin and metformin hydrochloride extended-release tablets can have other serious side effects. See "What are the possible side effects of saxagliptin and metformin hydrochloride extended-release tablets?"

2. Inflammation of the pancreas (pancreatitis) which may be severe and lead to death.

Certain medical problems make you more likely to get pancreatitis.

Before you start taking saxagliptin and metformin hydrochloride extended-release tablets:

Tell your healthcare provider if you have ever had:
- inflammation of your pancreas (pancreatitis)
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels

It is not known if having these medical problems will make you more likely to get pancreatitis with saxagliptin and metformin hydrochloride extended-release tablets.

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

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

Before you start taking saxagliptin and metformin hydrochloride extended-release tablets:

Tell your healthcare provider if you
- have ever had heart failure or have problems with your kidneys.

Contact your healthcare provider right away if you have any of the following symptoms:
- increasing shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- swelling or fluid retention, especially in the feet, ankles or legs
- unusual tiredness

These may be symptoms of heart failure.

What are saxagliptin and metformin hydrochloride extended-release tablets?
- Saxagliptin and metformin hydrochloride extended-release tablets are a prescription medicine that contains saxagliptin and metformin hydrochloride. Saxagliptin and metformin hydrochloride extended-release tablets are used with diet and exercise to help control high blood sugar (hyperglycemia) in adults with type 2 diabetes.
- Saxagliptin and metformin hydrochloride extended-release tablets are not for people with type 1 diabetes.
- Saxagliptin and metformin hydrochloride extended-release tablets are not for people with diabetic ketoacidosis (increased ketones in your blood or urine).

It is not known if saxagliptin and metformin hydrochloride extended-release tablets are safe and effective in children younger than 18 years old.

Who should not take saxagliptin and metformin hydrochloride extended-release tablets?

Do not take saxagliptin and metformin hydrochloride extended-release tablets if you:
- have kidney problems.
- are allergic to metformin hydrochloride, saxagliptin, or any of the ingredients in saxagliptin and metformin hydrochloride extended-release tablets. See the end of this Medication Guide for a complete list of ingredients in saxagliptin and metformin hydrochloride extended-release tablets.

  Symptoms of a serious allergic reaction to saxagliptin and metformin hydrochloride extended-release tablets may include:
  - swelling of your face, lips, throat, and other areas on your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)
  - skin rash, itching, flaking, or peeling

  If you have these symptoms, stop taking saxagliptin and metformin hydrochloride extended-release tablets and contact your healthcare provider right away.
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in your blood or urine).

Before taking saxagliptin and metformin hydrochloride extended-release tablets, tell your healthcare provider about all of your medical conditions, including if you:
- have type 1 diabetes. Saxagliptin and metformin hydrochloride extended-release tablets should not be used to treat type 1 diabetes.
- have a history or risk for diabetic ketoacidosis (high levels of certain acids, known as ketones, in the blood or urine). Saxagliptin and metformin hydrochloride extended-release tablets should not be used for the treatment of diabetic ketoacidosis.
- have kidney problems.
- have liver problems.
- have heart problems, including congestive heart failure.
- are older than 80 years. If you are over 80 years old you should not take saxagliptin and metformin hydrochloride extended-release tablets unless your kidneys have been checked and they are normal.
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking.
- are going to get an injection of dye or contrast agents for an x-ray procedure or if you are going to have surgery and will not be able to eat or drink much. In these situations, saxagliptin and metformin hydrochloride extended-release tablets may need to be stopped for a short time. Talk to your healthcare provider about when you should stop saxagliptin and metformin hydrochloride extended-release tablets and when you should start saxagliptin and metformin hydrochloride extended-release tablets again. See **"What is the most important information I should know about saxagliptin and metformin hydrochloride extended-release tablets?"**
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if saxagliptin and metformin hydrochloride extended-release tablets will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breast-feeding or plan to breast-feed. It is not known if saxagliptin and metformin hydrochloride extended-release passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby while you take saxagliptin and metformin hydrochloride extended-release tablets.

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

Body Mass Index

Saxagliptin

No dosage adjustment is recommended based on body mass index (BMI) which was not identified as a significant covariate on the apparent clearance of saxagliptin or its active metabolite in the population pharmacokinetic analysis.

Gender

Saxagliptin

No dosage adjustment is recommended based on gender. There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the active metabolite than males, but this difference is unlikely to be of clinical relevance. Gender was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between healthy subjects and patients with type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Geriatric

Saxagliptin

No dosage adjustment is recommended based on age alone. Elderly subjects (65 to 80 years) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively, for saxagliptin than young subjects (18 to 40 years). Differences in active metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the active metabolite in young and elderly subjects is likely due to multiple factors including declining renal function and metabolic capacity with increasing age. Age was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Metformin hydrochloride

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

Race and Ethnicity

Saxagliptin

No dosage adjustment is recommended based on race. The population pharmacokinetic analysis compared the pharmacokinetics of saxagliptin and its active metabolite in 309 Caucasian subjects with 105 non-Caucasian subjects (consisting of six racial groups). No significant difference in the pharmacokinetics of saxagliptin and its active metabolite were detected between these two populations.

Metformin hydrochloride

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

Drug Interaction Studies

Specific pharmacokinetic drug interaction studies with saxagliptin and metformin hydrochloride extended-release tablets have not been performed, although such studies have been conducted with the individual saxagliptin and metformin components.

In Vitro Assessment of Drug Interactions

In *in vitro* studies, saxagliptin and its active metabolite did not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, or 3A4. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is a P-glycoprotein (P-gp) substrate, but is not a significant inhibitor or inducer of P-gp.

In Vivo Assessment of Drug Interactions

Table 3: Effect of Coadministered Drug on Systemic Exposures of Saxagliptin and its Active Metabolite, 5-hydroxy Saxagliptin

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Metformin	1,000 mg	100 mg	Saxagliptin 5-hydroxy saxagliptin	0.98 0.99	0.79 0.88
Glyburide	5 mg	10 mg	Saxagliptin 5-hydroxy saxagliptin	0.98 ND	1.08 ND
Pioglitazone‡	45 mg QD for 10 days	10 mg QD for 5 days	saxagliptin 5-hydroxy saxagliptin	1.11 ND	1.11 ND
Digoxin	0.25 mg q6h first day followed by q12h second day followed by QD for 5 days	10 mg QD for 7 days	saxagliptin 5-hydroxy saxagliptin	1.05 1.06	0.99 1.02
Dapagliflozin	10 mg single dose	5 mg single dose	saxagliptin 5-hydroxy saxagliptin	↓1% ↑9%	↓7% ↑6%
Simvastatin	40 mg QD for 8 days	10 mg QD for 4 days	saxagliptin 5-hydroxy saxagliptin	1.12 1.02	1.21 1.08
Diltiazem	360 mg LA QD for 9 days	10 mg	saxagliptin 5-hydroxy saxagliptin	2.09 0.66	1.63 0.57
Rifampin§	600 mg QD for 6 days	5 mg	saxagliptin 5-hydroxy saxagliptin	0.24 1.03	0.47 1.39
Omeprazole	40 mg QD for 5 days	10 mg	saxagliptin 5-hydroxy saxagliptin	1.13 ND	0.98 ND
Aluminum hydroxide + magnesium hydroxide + simethicone	aluminum hydroxide: 2,400 mg magnesium hydroxide: 2,400 mg simethicone: 240 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	0.97 ND	0.74 ND
Famotidine	40 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	1.03 ND	1.14 ND
Limit saxagliptin and metformin hydrochloride extended-release tablets dose to 2.5 mg/1,000 mg once daily when coadministered with strong CYP3A4/5 inhibitors [*see Drug Interactions (7.1) and Dosage and Administration (2.2)*]:					
Ketoconazole	200 mg BID for 9 days	100 mg	saxagliptin 5-hydroxy saxagliptin	2.45 0.12	1.62 0.05
Ketoconazole	200 mg BID for 7 days	20 mg	saxagliptin 5-hydroxy saxagliptin	3.67 ND	2.44 ND

* Single dose unless otherwise noted. The 10 mg saxagliptin dose is not an approved dosage.

† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

‡ Results exclude one subject.

§ The plasma dipeptidyl peptidase-4 (DPP4) activity inhibition over a 24-hour dose interval was not affected by rifampin.

ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting.

Table 4: Effect of Saxagliptin on Systemic Exposures of Coadministered Drugs

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Geometric Mean Ratio (ratio with/without saxagliptin) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Metformin	1,000 mg	100 mg	metformin	1.20	1.09
Glyburide	5 mg	10 mg	glyburide	1.06	1.16
Pioglitazone‡	45 mg QD for 10 days	10 mg QD for 5 days	pioglitazone hydroxy-pioglitazone	1.08 ND	1.14 ND
Digoxin	0.25 mg q6h first day followed by q12h second day followed by QD for 5 days	10 mg QD for 7 days	digoxin	1.06	1.09
Simvastatin	40 mg QD for 8 days	10 mg QD for 4 days	simvastatin simvastatin acid	1.04 1.16	0.88 1.00
Diltiazem	360 mg LA QD for 9 days	10 mg	diltiazem	1.10	1.16
Ketoconazole	200 mg BID for 9 days	100 mg	ketoconazole	0.87	0.84
Ethinyl estradiol and norgestimate	ethinyl estradiol 0.035 mg and norgestimate 0.250 mg for 21 days	5 mg QD for 21 days	ethinyl estradiol norelgestromin norgestrel	1.07 1.10 1.13	0.98 1.09 1.17

* Single dose unless otherwise noted. The 10 mg saxagliptin dose is not an approved dosage.

† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

‡ Results include all subjects.

ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting.

Table 5: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Glyburide	5 mg	850 mg	metformin	0.91‡	0.93‡
Furosemide	40 mg	850 mg	metformin	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05‡	1.07‡
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin [*see Drug Interactions (7.3)*].					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61

* All metformin and coadministered drugs were given as single doses.

† AUC = AUC(INF)

‡ Ratio of arithmetic means

Table 6: Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without metformin) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Glyburide	5 mg	850 mg	glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	1.02
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	cimetidine	0.95§	1.01

* All metformin and coadministered drugs were given as single doses.

† AUC = AUC(INF) unless otherwise noted.

‡ Ratio of arithmetic means, p-value of difference <0.05.

§ AUC(0-24 hr) reported.

¶ Ratio of arithmetic means.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Saxagliptin and metformin hydrochloride extended-release tablets

No animal studies have been conducted with the combined products in saxagliptin and metformin hydrochloride extended-release tablets to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on studies with saxagliptin and metformin administered individually.

Saxagliptin

Carcinogenesis

Carcinogenicity was evaluated in 2-year studies conducted in CD-1 mice and Sprague-Dawley rats. Saxagliptin did not increase the incidence of tumors in mice dosed orally at 50, 250, and 600 mg/kg up to 870-times (males) and 1,165-times (females) the 5 mg/day clinical dose, based on AUC. Saxagliptin did not increase the incidence of tumors in rats dosed orally at 25, 75, 150, and 300 mg/kg up to 355-times (males) and 2,217-times (females) the 5 mg/day clinical dose, based on AUC.

Mutagenesis

Saxagliptin was not mutagenic or clastogenic in a battery of genotoxicity tests (Ames bacterial mutagenesis, human and rat lymphocyte cytogenetics, rat bone marrow micronucleus and DNA repair assays). The active metabolite of saxagliptin was not mutagenic in an Ames bacterial assay.

Impairment of Fertility

Saxagliptin administered to rats had no effect on fertility or the ability to maintain a litter at exposures up to 603-times and 776-times the 5 mg clinical dose in males and females, based on AUC.

Metformin hydrochloride

Carcinogenesis

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis

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.

Impairment of Fertility

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

13.2 Animal Toxicology and/or Pharmacology

Saxagliptin

Saxagliptin produced adverse skin changes in the extremities of cynomolgus monkeys (scabs and/or ulceration of tail, digits, scrotum, and/or nose). Skin lesions were reversible within exposure approximately 20-times the 5 mg clinical dose, but in some cases were irreversible and necrotizing at higher exposures. Adverse skin changes were not observed at exposures similar to (1-to 3-times) the 5 mg clinical dose. Clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

14 CLINICAL STUDIES

There have been no clinical efficacy or safety studies conducted with saxagliptin and metformin hydrochloride extended-release tablets to characterize its effect on A1C reduction. Bioequivalence of saxagliptin and metformin hydrochloride extended-release tablets with coadministered saxagliptin and metformin hydrochloride extended-release tablets has been demonstrated; however, relative bioavailability studies between saxagliptin and metformin hydrochloride extended-release tablets and coadministered saxagliptin and metformin hydrochloride immediate-release tablets have not been conducted. The metformin hydrochloride extended-release tablets and metformin hydrochloride immediate-release tablets have a similar extent of absorption (as measured by AUC) while peak plasma levels of extended-release tablets are approximately 20% lower than those of immediate-release tablets at the same dose.

14.1 Glycemic Efficacy Trials

The coadministration of saxagliptin and metformin immediate-release tablets has been studied in adults with type 2 diabetes inadequately controlled on metformin alone and in treatment-naive patients inadequately controlled on diet and exercise alone. In these two trials, treatment with saxagliptin dosed in the morning plus metformin immediate-release tablets at all doses produced clinically relevant and statistically significant improvements in A1C, fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG) following a standard oral glucose tolerance test (OGTT), compared to control. Reductions in A1C were seen across subgroups including gender, age, race, and baseline BMI.

In these two trials, decrease in body weight in the treatment groups given saxagliptin in combination with metformin immediate-release was similar to that in the groups given metformin immediate-release alone. Saxagliptin plus metformin immediate-release was not associated with significant changes from baseline in fasting serum lipids compared to metformin alone.

The coadministration of saxagliptin and metformin immediate-release tablets has also been evaluated in an active-controlled trial comparing add-on therapy with saxagliptin to glipizide in 858 patients inadequately controlled on metformin alone, in a placebo-controlled trial where a subgroup of 314 patients inadequately controlled on insulin plus metformin received add-on therapy with saxagliptin or placebo, a trial comparing saxagliptin to placebo in 257 patients inadequately controlled on metformin plus a sulfonylurea, and a trial comparing saxagliptin to placebo in 315 patients inadequately controlled on dapagliflozin and metformin.

In a 24-week, double-blind, randomized trial, patients treated with metformin immediate-release 500 mg twice daily for at least 8 weeks were randomized to continued treatment with metformin immediate-release 500 mg twice daily or to metformin extended-release either 1,000 mg once daily or 1,500 mg once daily. The mean change in A1C from baseline to Week 24 was 0.1% (95% confidence interval 0%, 0.3%) for the metformin immediate-release treatment arm, 0.3% (95% confidence interval 0.1%, 0.4%) for the 1,000 mg metformin extended-release treatment arm, and 0.1% (95% confidence interval 0%, 0.3%) for the 1,500 mg metformin extended-release treatment arm. Results of this trial suggest that patients receiving metformin immediate-release treatment may be safely switched to metformin extended-release once daily at the same total daily dose, up to 2,000 mg once daily. Following a switch from metformin immediate-release to metformin extended-release, glycemic control should be closely monitored and dosage adjustments made accordingly.

<u>Saxagliptin Morning and Evening Dosing</u>

A 24-week monotherapy trial was conducted to assess a range of dosing regimens for saxagliptin. Treatment-naive patients with inadequately controlled diabetes (A1C ≥7% to ≤10%) underwent a 2-week, single-blind diet, exercise, and placebo lead-in period. A total of 365 patients were randomized to 2.5 mg every morning, 5 mg every morning, 2.5 mg with possible titration to 5 mg every morning, or 5 mg every evening of saxagliptin, or placebo. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy added on to placebo or saxagliptin; the number of patients randomized per treatment group ranged from 71 to 74.

Treatment with either saxagliptin 5 mg every morning or 5 mg every evening provided significant improvements in A1C versus placebo (mean placebo-corrected reductions of −0.4% and −0.3%, respectively).

Coadministration of Saxagliptin with Metformin Immediate-Release in Treatment-Naive Patients

A total of 1,306 treatment-naive patients with type 2 diabetes mellitus participated in this 24-week, randomized, double-blind, active-controlled trial to evaluate the efficacy and safety of saxagliptin coadministered with metformin immediate-release in patients with inadequate glycemic control (A1C ≥8% to ≤12%) on diet and exercise alone. Patients were required to be treatment-naive to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, 1-week, dietary and exercise placebo lead-in period. Patients were randomized to one of four treatment arms: saxagliptin 5 mg + metformin immediate-release 500 mg, saxagliptin 10 mg + metformin immediate-release 500 mg, saxagliptin 10 mg + placebo, or metformin immediate-release 500 mg + placebo (the maximum recommended approved saxagliptin dose is 5 mg daily; the 10 mg daily dose of saxagliptin does not provide greater efficacy than the 5 mg daily dose and the 10 mg saxagliptin dosage is not an approved dosage). Saxagliptin was dosed once daily. In the 3 treatment groups using metformin immediate-release, the metformin dose was up-titrated weekly in 500 mg per day increments, as tolerated, to a maximum of 2,000 mg per day based on FPG. Patients who failed to meet specific glycemic goals during this study were treated with pioglitazone rescue as add-on therapy.

Coadministration of saxagliptin 5 mg plus metformin immediate-release provided significant improvements in A1C, FPG, and PPG compared with placebo plus metformin immediate-release (Table 7).

Table 7: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of Saxagliptin Coadministration with Metformin Immediate-Release in Treatment-Naive Patients*

Efficacy Parameter	Saxagliptin 5 mg + Metformin N=320	Placebo + Metformin N=328
Hemoglobin A1C (%)	**N=306**	**N=313**
Baseline (mean)	9.4	9.4
Change from baseline (adjusted mean†)	−2.5	−2.0
Difference from placebo + metformin (adjusted mean†)	−0.5‡	
95% Confidence Interval	(−0.7, −0.4)	
Percent of patients achieving A1C <7%	60%§ (185/307)	41% (129/314)
Fasting Plasma Glucose (mg/dL)	**N=315**	**N=320**
Baseline (mean)	199	199
Change from baseline (adjusted mean†)	−60	−47
Difference from placebo + metformin (adjusted mean†)	−13§	
95% Confidence Interval	(−19, −6)	
2-hour Postprandial Glucose (mg/dL)	**N=146**	**N=141**
Baseline (mean)	340	355
Change from baseline (adjusted mean†)	−138	−97
Difference from placebo + metformin (adjusted mean†)	−4§	
95% Confidence Interval	(−57, −25)	

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + metformin

§ p-value <0.05 compared to placebo + metformin

Addition of Saxagliptin to Metformin Immediate-Release

A total of 743 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin in combination with metformin immediate-release in patients with inadequate glycemic control (A1C ≥7% and ≤10%) on metformin alone. To qualify for enrollment, patients were required to be on a stable dose of metformin (1,500 to 2,550 mg daily) for at least 8 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin immediate-release at their pre-study dose, up to 2,500 mg daily, for the duration of the study. Following the lead-in period, eligible patients were randomized to 2.5 mg, 5 mg, or 10 mg of saxagliptin or placebo in addition to their current dose of open-label metformin immediate-release (the maximum recommended approved saxagliptin dose is 5 mg daily; the 10 mg daily dose of saxagliptin does not provide greater efficacy than the 5 mg daily dose and the 10 mg dosage is not an approved dosage). Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue therapy, added on to existing study medications. Dose titrations of saxagliptin and metformin immediate-release were not permitted.

Saxagliptin 2.5 mg and 5 mg add-on to metformin immediate-release provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to metformin immediate-release (Table 8). Mean changes from baseline for A1C over time and at endpoint are shown in Figure 1. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 15% in the saxagliptin 2.5 mg add-on to metformin immediate-release group, 13% in the saxagliptin 5 mg add-on to metformin immediate-release group, and 27% in the placebo add-on to metformin immediate-release group.

Table 8: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of Saxagliptin as Add-On Combination Therapy with Metformin Immediate-Release*

Efficacy Parameter	Saxagliptin 2.5 mg + Metformin N=192	Saxagliptin 5 mg + Metformin N=191	Placebo + Metformin N=179
Hemoglobin A1C (%)	**N=186**	**N=186**	**N=175**
Baseline (mean)	8.1	8.1	8.1
Change from baseline (adjusted mean†)	−0.6	−0.7	+0.1
Difference from placebo (adjusted mean†)	−0.7‡	−0.8‡	
95% Confidence Interval	(−0.9, −0.5)	(−1.0, −0.6)	
Percent of patients achieving A1C <7%	37%§ (69/186)	44%§ (81/186)	17% (29/175)
Fasting Plasma Glucose (mg/dL)	**N=188**	**N=187**	**N=176**
Baseline (mean)	174	179	175
Change from baseline (adjusted mean†)	−14	−22	+1
Difference from placebo (adjusted mean†)	−16§	−23§	
95% Confidence Interval	(−23, −9)	(−30, −16)	
2-hour Postprandial Glucose (mg/dL)	**N=155**	**N=155**	**N=135**
Baseline (mean)	294	296	295
Change from baseline (adjusted mean†)	−62	−58	−18
Difference from placebo (adjusted mean†)	−44§	−40§	
95% Confidence Interval	(−60, −27)	(−56, −24)	

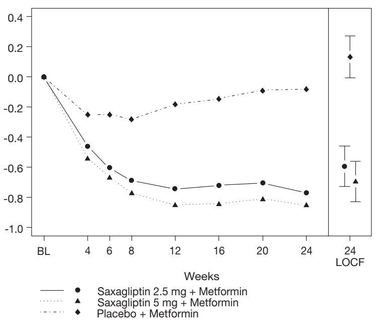
* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + metformin.

§ p-value <0.05 compared to placebo + metformin.

Figure 1: Mean Change from Baseline in A1C in a Placebo-Controlled Trial of Saxagliptin as Add-On Combination Therapy with Metformin Immediate-Release*



* Includes patients with a baseline and week 24 value.

Week 24 (LOCF) includes intent-to-treat population using last observation on study prior to pioglitazone rescue therapy for patients needing rescue. Mean change from baseline is adjusted for baseline value.

Saxagliptin Add-On Combination Therapy with Metformin Immediate-Release versus Glipizide Add-On Combination Therapy with Metformin Immediate-Release

In this 52-week, active-controlled trial, a total of 858 patients with type 2 diabetes and inadequate glycemic control (A1C >6.5% and ≤10%) on metformin immediate-release alone were randomized to double-blind add-on therapy with saxagliptin or glipizide. Patients were required to be on a stable dose of metformin immediate-release (at least 1,500 mg daily) for at least 8 weeks prior to enrollment.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin immediate-release (1,500 to 3,000 mg based on their prestudy dose). Following the lead-in period, eligible patients were randomized to 5 mg of saxagliptin or 5 mg of glipizide in addition to their current dose of open-label metformin immediate-release. Patients in the glipizide plus metformin immediate-release group underwent blinded titration of the glipizide dose during the first 18 weeks of the trial up to a maximum glipizide dose of 20 mg per day. Titration was based on a goal FPG ≤110 mg/dL or the highest tolerable glipizide dose. Fifty percent (50%) of the glipizide-treated patients were titrated to the 20-mg daily dose; 21% of the glipizide-treated patients had a final daily glipizide dose of 5 mg or less. The mean final daily dose of glipizide was 15 mg.

After 52 weeks of treatment, saxagliptin and glipizide resulted in similar mean reductions from baseline in A1C when added to metformin immediate-release therapy (Table 9). This conclusion may be limited to patients with baseline A1C comparable to those in the trial (91% of patients had baseline A1C <9%).

From a baseline mean body weight of 89 kg, there was a statistically significant mean reduction of 1.1 kg in patients treated with saxagliptin compared to a mean weight gain of 1.1 kg in patients treated with glipizide (p<0.0001).

Table 9: Glycemic Parameters at Week 52 in an Active-Controlled Trial of Saxagliptin versus Glipizide in Combination with Metformin Immediate-Release*

Efficacy Parameter	Saxagliptin 5 mg + Metformin N=428	Titrated Glipizide + Metformin N=430
Hemoglobin A1C (%)	**N=423**	**N=423**
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean†)	−0.6	−0.7
Difference from glipizide + metformin (adjusted mean†)	0.1	
95% Confidence Interval	(−0.02, 0.2)‡	
Fasting Plasma Glucose (mg/dL)	**N=420**	**N=420**
Baseline (mean)	162	161
Change from baseline (adjusted mean†)	−9	−16
Difference from glipizide + metformin (adjusted mean†)	6	
95% Confidence Interval	(2, 11)§	

* Intent-to-treat population using last observation on study.

† Least squares mean adjusted for baseline value.

‡ Saxagliptin + metformin is considered non-inferior to glipizide + metformin because the upper limit of this confidence interval is less than the prespecified non-inferiority margin of 0.35%.

§ Significance not tested.

Saxagliptin Add-On Combination Therapy with Insulin (with or without Metformin Immediate-Release)

A total of 455 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin in combination with insulin in patients with inadequate glycemic control (A1C ≥7.5% and ≤11%) on insulin alone (N=141) or on insulin in combination with a stable dose of metformin immediate-release (N=314). Patients were required to be on a stable dose of insulin (≥30 units to ≤150 units daily) with ≤20% variation in total daily dose for ≥8 weeks prior to screening. Patients entered the trial on intermediate- or long-acting (basal) insulin or premixed insulin. Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a premixed insulin.

Patients who met eligibility criteria were enrolled in a single-blind, four-week, dietary and exercise placebo lead-in period during which patients received insulin (and metformin immediate-release if applicable) at their pretrial dose(s). Following the lead-in period, eligible patients were randomized to add-on therapy with either saxagliptin 5 mg or placebo. Doses of the antidiabetic therapies were to remain stable but patients were rescued and allowed to adjust the insulin regimen if specific glycemic goals were not met or if the investigator learned that the patient had self-increased the insulin dose by >20%. Data after rescue were excluded from the primary efficacy analyses.

Add-on therapy with saxagliptin 5 mg provided significant improvements from baseline to Week 24 in A1C and PPG compared with add-on placebo (Table 10). Similar mean reductions in A1C versus placebo were observed for patients using saxagliptin 5 mg add-on to insulin alone and saxagliptin 5 mg add-on to insulin in combination with metformin immediate-release (−0.4% and −0.4%, respectively). The percentage of patients who discontinued for lack of glycemic control or who were rescued was 23% in the saxagliptin group and 32% in the placebo group.

The mean daily insulin dose at baseline was 53 units in patients treated with saxagliptin 5 mg and 55 units in patients treated with placebo. The mean change from baseline in daily dose of insulin was 2 units for the saxagliptin 5 mg group and 5 units for the placebo group.

Table 10: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of Saxagliptin as Add-On Combination Therapy with Insulin*

Efficacy Parameter	Saxagliptin 5 mg + Insulin (+/− Metformin) N=304	Placebo + Insulin (+/− Metformin) N=151
Hemoglobin A1C (%)	**N=300**	**N=149**
Baseline (mean)	8.7	8.7
Change from baseline (adjusted mean†)	−0.7	−0.3
Difference from placebo (adjusted mean†)	−0.4‡	
95% Confidence Interval	(−0.6, −0.2)	
2-hour Postprandial Glucose (mg/dL)	**N=262**	**N=129**
Baseline (mean)	251	255
Change from baseline (adjusted mean†)	−27	−4
Difference from placebo (adjusted mean†)	−23§	
95% Confidence Interval	(−37, −9)	

* Intent-to-treat population using last observation on study or last observation prior to insulin rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value and metformin use at baseline.

‡ p-value <0.0001 compared to placebo + insulin.

§ p-value <0.05 compared to placebo + insulin.

The change in fasting plasma glucose from baseline to Week 24 was also tested, but was not statistically significant. The percent of patients achieving an A1C <7% was 17% (52/300) with saxagliptin in combination with insulin compared to 7% (10/149) with placebo. Significance was not tested.

Saxagliptin Add-On Combination Therapy with Metformin plus Sulfonylurea

A total of 257 subjects with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin in combination with metformin plus a sulfonylurea in patients with inadequate glycemic control (A1C ≥7% and ≤10%). Patients were to be on a stable combined dose of metformin extended-release or immediate-release (at maximum tolerated dose, with minimum dose for enrollment being 1,500 mg) and a sulfonylurea (at maximum tolerated dose, with minimum dose for enrollment being ≥50% of the maximum recommended dose) for ≥8 weeks prior to enrollment.

Patients who met eligibility criteria were entered in a 2-week enrollment period to allow assessment of inclusion/exclusion criteria. Following the 2-week enrollment period, eligible patients were randomized to either double-blind saxagliptin (5 mg once daily) or double-blind matching placebo for 24 weeks. During the 24-week double-blind treatment period, patients were to receive metformin and a sulfonylurea at the same constant dose ascertained during enrollment. Sulfonylurea dose could be down titrated once in the case of a major hypoglycemic event or recurring minor hypoglycemic events. In the absence of hypoglycemia, titration (up or down) of study medication during the treatment period was prohibited.

Saxagliptin in combination with metformin plus a sulfonylurea provided significant improvements in A1C and PPG compared with placebo in combination with metformin plus a sulfonylurea (Table 11). The percentage of patients who discontinued for lack of glycemic control was 6% in the saxagliptin group and 5% in the placebo group.

Table 11: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of Saxagliptin as Add-On Combination Therapy with Metformin plus Sulfonylurea*

Efficacy Parameter	Saxagliptin 5 mg + Metformin plus Sulfonylurea N=129	Placebo + Metformin plus Sulfonylurea N=128
Hemoglobin A1C (%)	**N=127**	**N=127**
Baseline (mean)	8.4	8.2
Change from baseline (adjusted mean†)	−0.7	−0.1
Difference from placebo (adjusted mean†)	−0.7‡	
95% Confidence Interval	(−0.9, −0.5)	
2-hour Postprandial Glucose (mg/dL)	**N=115**	**N=113**
Baseline (mean)	268	262
Change from baseline (adjusted mean†)	−12	5
Difference from placebo (adjusted mean†)	−17§	
95% Confidence Interval	(−32, −2)	

* Intent-to-treat population using last observation prior to discontinuation.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + metformin plus sulfonylurea

§ p-value <0.05 compared to placebo + metformin plus sulfonylurea.

The change in fasting plasma glucose from baseline to Week 24 was also tested, but was not statistically significant. The percent of patients achieving an A1C <7% was 31% (39/127) with saxagliptin in combination with metformin plus a sulfonylurea compared to 9% (12/127) with placebo. Significance was not tested.

Saxagliptin Add-on Combination Therapy with Metformin plus an SGLT2 Inhibitor

A total of 315 patients with type 2 diabetes participated in this 24-week randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin added to dapagliflozin (an SGLT2 inhibitor) and metformin in patients with a baseline of HbA1c ≥7% to ≤10.5%. The mean age of these subjects was 54.6 years, 1.6% were 75 years or older and 52.7% were female. The population was 87.9% White, 6.3% Black or African American, 4.1% Asian, and 1.6% Other race. At baseline the population had diabetes for an average of 7.7 years and a mean HbA1c of 7.9%. The mean eGFR at baseline was 93.4 mL/min/1.73 m². Patients were required to be on a stable dose of metformin (≥1,500 mg per day) for at least 8 weeks prior to enrollment. Eligible subjects who completed the screening period entered the lead in treatment period, which included 16 weeks of open-label metformin and 10 mg dapagliflozin treatment. Following the lead-in period, eligible patients were randomized to saxagliptin 5 mg (N=153) or placebo (N=162).

The group treated with add-on saxagliptin had statistically significant greater reductions in HbA1c from baseline versus the group treated with placebo (see Table 12).

Table 12: HbA1c Change from Baseline at Week 24 in a Placebo-Controlled Trial of Saxagliptin as Add-On to Dapagliflozin and Metformin§

	Saxagliptin 5 mg (N=153)†	Placebo (N=162)†
	In combination with Dapagliflozin and Metformin	
Hemoglobin A1C (%)*		
Baseline (mean)	8.0	7.9
Change from baseline (adjusted mean‡) 95% Confidence Interval	-0.5 (-0.6, -0.4)	-0.2 (-0.3, -0.1)
Difference from placebo (adjusted mean) 95% Confidence Interval	-0.4¶ (-0.5, -0.2)	

* Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputation to model washout of the treatment effect using placebo data for all subjects having missing week 24 data.

† Number of randomized and treated patients.

‡ Least squares mean adjusted for baseline value.

§ There were 6.5% (n=10) of randomized subjects in the saxagliptin arm and 3.1% (n=5) in the placebo arm for whom change from baseline HbA1c data was missing at week 24. Of the subjects who discontinued study medication early, 9.1% (1 of 11) in the saxagliptin arm and 16.7% (1 of 6) in the placebo arm had HbA1c measured at week 24.

¶ p-value <0.0001

The known proportion of patients achieving HbA1c <7% at Week 24 was 35.3% in the saxagliptin treated group compared to 23.1% in the placebo treated group.

14.2 Cardiovascular Safety Trial

The cardiovascular risk of saxagliptin was evaluated in SAVOR, a multicenter, multinational, randomized, double-blind study comparing saxagliptin (N=8280) to placebo (N=8212), both administered in combination with standard of care, in adult patients with type 2 diabetes at high risk for atherosclerotic cardiovascular disease. Of the randomized study subjects, 97.5% completed the trial, and the median duration of follow-up was approximately 2 years. The trial was event-driven, and patients were followed until a sufficient number of events were accrued.

Subjects were at least 40 years of age, had A1C ≥6.5%, and multiple risk factors (21% of randomized subjects) for cardiovascular disease (age ≥55 years for men and ≥60 years for women plus at least one additional risk factor of dyslipidemia, hypertension, or current cigarette smoking) or established (79% of the randomized subjects) cardiovascular disease defined as a history of ischemic heart disease, peripheral vascular disease, or ischemic stroke. The majority of subjects were male (67%) and Caucasian (75%) with a mean age of 65 years. Approximately 16% of the population had moderate (estimated glomerular filtration rate [eGFR] ≥30 to ≤50 mL/min) to severe (eGFR <30 mL/min) renal impairment, and 13% had a prior history of heart failure. Subjects had a median duration of type 2 diabetes mellitus of approximately 10 years, and a mean baseline A1C level of 8%. Approximately 5% of subjects were treated with diet and exercise only at baseline. Overall, the use of diabetes medications was balanced across treatment groups (metformin 69%, insulin 41%, sulfonylureas 40%, and TZDs 6%). The use of cardiovascular disease medications was also balanced (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs] 79%, statins 78%, aspirin 75%, beta-blockers 62%, and non-aspirin antiplatelet medications 24%).

The primary analysis in SAVOR was time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event in SAVOR was defined as a cardiovascular death, or a nonfatal myocardial infarction (MI) or a nonfatal ischemic stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE, and was also powered for a superiority comparison if non-inferiority was demonstrated.

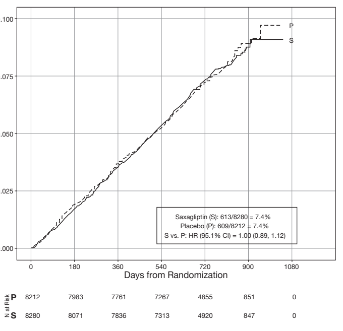
The results of SAVOR, including the contribution of each component to the primary composite endpoint are shown in Table 13. The incidence rate of MACE was similar in both treatment arms: 3.8 MACE per 100 patient-years on placebo vs. 3.8 MACE per 100 patient-years on saxagliptin. The estimated hazard ratio of MACE associated with saxagliptin relative to placebo was 1.00 with a 95.1% confidence interval of (0.89, 1.12). The upper bound of this confidence interval, 1.12, excluded a risk margin larger than 1.3.

Table 13: Major Adverse Cardiovascular Events (MACE) by Treatment Group in the SAVOR Trial

	Saxagliptin		Placebo		Hazard Ratio
	Number of Subjects (%)	Rate per 100 PY	Number of Subjects (%)	Rate per 100 PY	(95.1% CI)
Composite of first event of CV death, non-fatal MI or non-fatal ischemic stroke (MACE)	**N=8280**	**Total PY = 16308.8**	**N=8212**	**Total PY = 16156.0**	
	613 (7.4)	3.8	609 (7.4)	3.8	1.00 (0.89, 1.12)
CV death	245 (3.0)	1.5	234 (2.8)	1.4	
Non-fatal MI	233 (2.8)	1.4	260 (3.2)	1.6	
Non-fatal ischemic stroke	135 (1.6)	0.8	115 (1.4)	0.7	

The Kaplan-Meier-based cumulative event probability is presented in Figure 2 for time to first occurrence of the primary MACE composite endpoint by treatment arm. The curves for both saxagliptin and placebo arms are close together throughout the duration of the trial. The estimated cumulative event probability is approximately linear for both arms, indicating that the incidence of MACE for both arms was constant over the trial duration.

Figure 2: Cumulative Percent of Time to First MACE



Vital status was obtained for 99% of subjects in the trial. There were 798 deaths in the SAVOR trial. Numerically more patients (5.1%) died in the saxagliptin group than in the placebo group (4.6%). The risk of deaths from all cause (Table 14) was not statistically different between the treatment groups (HR: 1.11; 95.1% CI: 0.96, 1.27).

Table 14: All-Cause Mortality by Treatment Group in the SAVOR Study

	Saxagliptin		Placebo		Hazard Ratio
	Number of Subjects (%)	Rate per 100 PY	Number of Subjects (%)	Rate per 100 PY	(95.1% CI)
	N=8280	**PY = 16645.3**	**N=8212**	**PY = 16531.5**	
All-cause mortality	420 (5.1)	2.5	378 (4.6)	2.3	1.11 (0.96, 1.27)
CV death	269 (3.2)	1.6	260 (3.2)	1.6	
Non-CV death	151 (1.8)	0.9	118 (1.4)	0.7	

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Saxagliptin and metformin hydrochloride extended-release tablets are available as follows:

Saxagliptin and metformin hydrochloride extended-release tablets 5 mg/500 mg are light brown to brown colored, capsule shaped film-coated tablets imprinted with SM3 on one side and plain on other side and free from physical defects. They are available in packages as listed below.

Bottles of 30	43598-620-30
Bottles of 100	43598-620-01

Saxagliptin and metformin hydrochloride extended-release tablets 5 mg/1,000 mg are pink, colored, modified oval shaped film-coated tablets imprinted with SM2 on one side and plain on other side and free from physical defects. They are available in packages as listed below.

Bottles of 30	43598-619-30
Bottles of 100	43598-619-01

Saxagliptin and metformin hydrochloride extended-release tablets 2.5 mg/1,000 mg are pale yellow to light yellow colored, modified oval shaped film-coated tablets imprinted with SM1 on one side and plain on other side and free from physical defects. They are available in packages as listed below.

Bottles of 30	43598-618-30
Bottles of 60	43598-618-60
Bottles of 100	43598-618-01

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Medication Guide

Healthcare providers should instruct their patients to read the Medication Guide before starting saxagliptin and metformin hydrochloride extended-release tablet therapy and to reread it each time the prescription is renewed. Patients should be instructed to inform their healthcare provider if they develop any unusual symptom or if any existing symptom persists or worsens.

Patients should be informed of the potential risks and benefits of saxagliptin and metformin hydrochloride extended-release tablets and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Lactic Acidosis

The risks of lactic acidosis due to the metformin component, its symptoms and conditions that predispose to its development, as noted in *Warnings and Precautions (5.1),* should be explained to patients. Patients should be advised to discontinue saxagliptin and metformin hydrochloride extended-release tablets immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgia, malaise, unusual somnolence, dizziness, slow or irregular heartbeat, sensation of feeling cold (especially in the extremities), or other nonspecific symptoms occur. Gastrointestinal symptoms are common during initiation of metformin treatment and may occur during initiation of saxagliptin and metformin hydrochloride extended-release tablets therapy; however, patients should consult their physician if they develop unexplained symptoms. Although gastrointestinal symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to lactic acidosis or other serious disease.

Patients should be counseled against excessive alcohol intake while receiving saxagliptin and metformin hydrochloride extended-release tablets.

Patients should be informed about the importance of regular testing of renal function and hematological parameters when receiving treatment with saxagliptin and metformin hydrochloride extended-release tablets.

Instruct patients to inform their doctor that they are taking saxagliptin and metformin hydrochloride extended-release tablets prior to any surgical or radiological procedure, as temporary discontinuation of saxagliptin and metformin hydrochloride extended-release tablets may be required until renal function has been confirmed to be normal [*see Warnings and Precautions (5.1)*].

Pancreatitis

Patients should be informed that acute pancreatitis has been reported during post-marketing use of saxagliptin. Before initiating saxagliptin and metformin hydrochloride extended-release tablets, patients should be questioned about other risk factors for pancreatitis, such as a history of pancreatitis, alcoholism, gallstones, or hypertriglyceridemia. Patients should also be informed that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue saxagliptin and metformin hydrochloride extended-release tablets and contact their healthcare provider if persistent severe abdominal pain occurs [see *Warnings and Precautions (5.2)*].

Heart Failure

Patients should be informed of the signs and symptoms of heart failure. Before initiating saxagliptin and metformin hydrochloride extended-release tablets, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Patients should be instructed to contact their healthcare provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet [*see Warnings and Precautions (5.3)*].

Hypoglycemia

Patients should be informed that the incidence of hypoglycemia may be increased when saxagliptin and metformin hydrochloride extended-release tablets are added to an insulin secretagogue (e.g., sulfonylurea) or insulin.

Hypersensitivity Reactions

Patients should be informed that serious allergic (hypersensitivity) reactions, such as angioedema, anaphylaxis, and exfoliative skin conditions, have been reported during post-marketing use of saxagliptin. If symptoms of these allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking saxagliptin and metformin hydrochloride extended-release tablets and seek medical advice promptly.

Severe and Disabling Arthralgia

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

Bullous Pemphigoid

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

Administration Instructions

Patients should be informed that saxagliptin and metformin hydrochloride extended-release tablets must be swallowed whole and not crushed or chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

Missed Dose

Patients should be informed that if they miss a dose of saxagliptin and metformin hydrochloride extended-release tablets, they should take the next dose as prescribed, unless otherwise instructed by their healthcare provider. Patients should be instructed not to take an extra dose the next day.

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Dr.Reddy's

MEDICATION GUIDE

Saxagliptin and Metformin Hydrochloride
(sax-a-GLIP-tin and met-FOR-min hye-droe-KLOR-ide)
Extended-Release Tablets, for oral use

What is the most important information I should know about saxagliptin and metformin hydrochloride extended-release tablets?

Serious side effects can happen in people taking saxagliptin and metformin hydrochloride extended-release tablets, including:

1. **Lactic acidosis. Metformin, one of the medicines in saxagliptin and metformin hydrochloride extended-release tablets, can cause a rare but serious condition called lactic acidosis (a build-up of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.**

Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:

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

Most people who have had lactic acidosis with metformin have other things that, combined with the metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with saxagliptin and metformin hydrochloride extended-release tablets if you:

- have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye
- have liver problems
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids
- have surgery
- have a heart attack, severe infection, or stroke

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your saxagliptin and metformin hydrochloride extended-release tablets for a while if you have any of these things.

Saxagliptin and metformin hydrochloride extended-release tablets can have other serious side effects. See "What are the possible side effects of saxagliptin and metformin hydrochloride extended-release tablets?

2. **Inflammation of the pancreas (pancreatitis)** which may be severe and lead to death.
   Certain medical problems make you more likely to get pancreatitis.
   Before you start taking saxagliptin and metformin hydrochloride extended-release tablets:
   Tell your healthcare provider if you have ever had:
   - inflammation of your pancreas (pancreatitis)
   - stones in your gallbladder (gallstones)
   - a history of alcoholism
   - high blood triglyceride levels

   It is not known if having these medical problems will make you more likely to get pancreatitis with saxagliptin and metformin hydrochloride extended-release tablets.

   Stop taking saxagliptin and metformin hydrochloride extended-release tablets and contact your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.
3. **Heart failure.** Heart failure means your heart does not pump blood well enough.
   Before you start taking saxagliptin and metformin hydrochloride extended-release tablets:
   Tell your healthcare provider if you
   - have ever had heart failure or have problems with your kidneys.

   Contact your healthcare provider right away if you have any of the following symptoms:
   - increasing shortness of breath or trouble breathing, especially when you lie down
   - an unusually fast increase in weight
   - swelling or fluid retention, especially in the feet, ankles or legs
   - unusual tiredness

   These may be symptoms of heart failure.

What are saxagliptin and metformin hydrochloride extended-release tablets?

- Saxagliptin and metformin hydrochloride extended-release tablets are a prescription medicine that contains saxagliptin and metformin hydrochloride. Saxagliptin and metformin hydrochloride extended-release tablets are used with diet and exercise to help control high blood sugar (hyperglycemia) in adults with type 2 diabetes.
- Saxagliptin and metformin hydrochloride extended-release tablets are not for people with type 1 diabetes.
- Saxagliptin and metformin hydrochloride extended-release tablets are not for people with diabetic ketoacidosis (increased ketones in your blood or urine).

It is not known if saxagliptin and metformin hydrochloride extended-release tablets are safe and effective in children younger than 18 years old.

Who should not take saxagliptin and metformin hydrochloride extended-release tablets?

Do not take saxagliptin and metformin hydrochloride extended-release tablets if you:

- have kidney problems.
- are allergic to metformin hydrochloride, saxagliptin, or any of the ingredients in saxagliptin and metformin hydrochloride extended-release tablets. See the end of this Medication Guide for a complete list of ingredients in saxagliptin and metformin hydrochloride extended-release tablets.
  Symptoms of a serious allergic reaction to saxagliptin and metformin hydrochloride extended-release tablets may include:
  - swelling of your face, lips, throat, and other areas on your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)
  - skin rash, itching, flaking, or peeling

  If you have these symptoms, stop taking saxagliptin and metformin hydrochloride extended-release tablets and contact your healthcare provider right away.
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in your blood or urine).

Before taking saxagliptin and metformin hydrochloride extended-release tablets, tell your healthcare provider about all of your medical conditions, including if you:

- have type 1 diabetes. Saxagliptin and metformin hydrochloride extended-release tablets should not be used to treat type 1 diabetes.
- have a history or risk for diabetic ketoacidosis (high levels of certain acids, known as ketones, in the blood or urine). Saxagliptin and metformin hydrochloride extended-release tablets should not be used for the treatment of diabetic ketoacidosis.
- have kidney problems.
- have liver problems.
- have heart problems, including congestive heart failure.
- are older than 80 years. If you are over 80 years old you should not take saxagliptin and metformin hydrochloride extended-release tablets unless your kidneys have been checked and they are normal.
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking.
- are going to get an injection of dye or contrast agents for an x-ray procedure or if you are going to have surgery and will not be able to eat or drink much. In these situations, saxagliptin and metformin hydrochloride extended-release tablets may need to be stopped for a short time. Talk to your healthcare provider about when you should stop saxagliptin and metformin hydrochloride extended-release tablets and when you should start saxagliptin and metformin hydrochloride extended-release tablets again. See "**What is the most important information I should know about saxagliptin and metformin hydrochloride extended-release tablets?**"
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if saxagliptin and metformin hydrochloride extended-release tablets will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breast-feeding or plan to breast-feed. It is not known if saxagliptin and metformin hydrochloride extended-release passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby while you take saxagliptin and metformin hydrochloride extended-release tablets.

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

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine. Saxagliptin and metformin hydrochloride extended-release tablets may affect the way other medicines work, and other medicines may affect how saxagliptin and metformin hydrochloride extended-release tablets work.

Tell your healthcare provider if you will be starting or stopping certain other types of medicines, such as antibiotics, or medicines that treat fungus or HIV/AIDS, because your dose of saxagliptin and metformin hydrochloride extended-release tablets might need to be changed.

How should I take saxagliptin and metformin hydrochloride extended-release tablets?

- Take saxagliptin and metformin hydrochloride extended-release tablets exactly as your healthcare provider tells you.
- Saxagliptin and metformin hydrochloride extended-release tablets should be taken with meals to help lessen an upset stomach side effect.
- Swallow saxagliptin and metformin hydrochloride extended-release tablets whole. Do not crush, cut, or chew saxagliptin and metformin hydrochloride extended-release tablets.
- You may sometimes pass a soft mass in your stools (bowel movement) that looks like saxagliptin and metformin hydrochloride extended-release tablets.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your healthcare provider right away if you have any of these problems.
- Your healthcare provider should do blood tests to check how well your kidneys are working before and during your treatment with saxagliptin and metformin hydrochloride extended-release tablets.
- Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Follow your healthcare provider's instructions for treating blood sugar that is too low (hypoglycemia). Talk to your healthcare provider if low blood sugar is a problem for you. See "**What are the possible side effects of saxagliptin and metformin hydrochloride extended-release tablets?**"
- Check your blood sugar as your healthcare provider tells you to.
- Stay on your prescribed diet and exercise program while taking saxagliptin and metformin hydrochloride extended-release tablets.
- If you miss a dose of saxagliptin and metformin hydrochloride extended-release tablets, take your next dose as prescribed unless your healthcare provider tells you differently. Do not take an extra dose the next day.
- If you take too many saxagliptin and metformin hydrochloride extended-release tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of saxagliptin and metformin hydrochloride extended-release tablets?

Saxagliptin and metformin hydrochloride extended-release tablets can cause serious side effects, including:

- See "**What is the most important information I should know about saxagliptin and metformin hydrochloride extended-release tablets?**"
- **Allergic (hypersensitivity) reactions, such as:**
  - swelling of your face, lips, throat, and other areas on your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)
  - skin rash, itching, flaking, or peeling

  If you have these symptoms, stop taking saxagliptin and metformin hydrochloride extended-release tablets and contact your healthcare provider right away.
- **Low blood sugar (hypoglycemia).** May become worse in people who also take another medication to treat diabetes, such as sulfonylureas or insulin. Tell your healthcare provider if you take other diabetes medicines. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your healthcare provider. Symptoms of low blood sugar include:
  - shaking
  - sweating
  - rapid heartbeat
  - change in vision
  - hunger
  - headache
  - change in mood
- **Joint pain.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in saxagliptin and metformin hydrochloride extended-release tablets, may develop joint pain that can be severe. Call your healthcare provider if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in saxagliptin and metformin hydrochloride extended-release tablets, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your healthcare provider right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your healthcare provider may tell you to stop taking saxagliptin and metformin hydrochloride extended-release tablets.

Common side effects of saxagliptin and metformin hydrochloride extended-release tablets include:

- upper respiratory tract infection
- stuffy or runny nose and sore throat
- urinary tract infection
- headache
- diarrhea
- nausea and vomiting

Taking saxagliptin and metformin hydrochloride extended-release tablets with meals can help lessen the common stomach side effects of metformin. If you have unexplained stomach problems, tell your healthcare provider. Stomach problems that start later during treatment may be a sign of something more serious.

These are not all of the possible side effects of saxagliptin and metformin hydrochloride extended-release tablets.

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

How should I store saxagliptin and metformin hydrochloride extended-release tablets?

Store saxagliptin and metformin hydrochloride extended-release tablets at 20°C to 25°C (68°F to 77°F).

Keep saxagliptin and metformin hydrochloride extended-release tablets and all medicines out of the reach of children.

General information about the use of saxagliptin and metformin hydrochloride extended-release tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use saxagliptin and metformin hydrochloride extended-release tablets for a condition for which they were not prescribed. Do not give saxagliptin and metformin hydrochloride extended-release tablets to other people, even if they have the same symptoms you have. They may harm them.

You can ask your pharmacist or healthcare provider for information about saxagliptin and metformin hydrochloride extended-release tablets that is written for health professionals.

What are the ingredients of saxagliptin and metformin hydrochloride extended-release tablets?

Active ingredients: saxagliptin and metformin hydrochloride.

Inactive ingredients in each tablet: colloidal silicon dioxide, hydrochloric acid, hypromellose, iron oxide black, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, propylene glycol, shellac, talc, titanium dioxide. In addition, 5 mg/500 mg tablets contain iron oxide red and iron oxide yellow; 5 mg/1,000 mg tablets contain iron oxide red; 2.5 mg/1,000 mg tablets contain iron oxide yellow.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems. The main goal of treating diabetes is to lower your blood sugar so that it is as close to normal as possible. High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

Talk to your healthcare provider about how to prevent, recognize, and take care of low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.

For more information, call 1-888-375-3784.

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

To reorder additional Medication Guides, contact Dr. Reddy's Customer Service at 1-866-733-3952.

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