Alogliptin and Metformin HCl Tablets

P116-04

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALOGLIPTIN AND METFORMIN HCL TABLETS safely and effectively. See full prescribing information for ALOGLIPTIN AND METFORMIN HCL TABLETS.

Alogliptin and Metformin HCl Tablets, for oral use

Initial U.S. Approval: 2013

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally greater than 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 alogliptin and metformin HCl tablets and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

------------RECENT MAJOR CHANGES------------

Boxed Warning	12/2016
Indications and Usage (1.1)	4/2016
Dosage and Administration	
Recommendations for Use in Renal Impairment (2.2)	5/2016
Discontinuation for Iodinated Contrast Imaging Procedures (2.3)	5/2016
Contraindications (4)	5/2016
Warnings and Precautions	
Lactic Acidosis (5.1)	12/2016
Pancreatitis (5.2)	4/2016
Heart Failure (5.3)	4/2016
Hepatic Effects (5.5)	4/2016
Bullous Pemphigoid (5.9)	12/2016

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

Alogliptin and metformin HCl tablets are a dipeptidyl-peptidase-4 (DPP-4) inhibitor and a biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1.1)

Important Limitations of Use: Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1.1)

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

- Individualize the starting dose based on the patient's current regimen. (2.1)
- Give twice daily with food. (2.1)
- Adjust the dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg alogliptin and 2000 mg metformin HCl. (2.1)
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR). (2.2)
  - Do not use in patients with eGFR below 60 mL/min/1.73 m².
- Alogliptin and metformin HCl tablets may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.3)

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

Tablets: 12.5 mg alogliptin and 500 mg metformin HCl, 12.5 mg alogliptin and 1000 mg metformin HCl. (3)

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

- Severe renal impairment: eGFR below 30 mL/min/1.73 m². (4)
- Metabolic acidosis, including diabetic ketoacidosis. (4)
- History of a serious hypersensitivity reaction to alogliptin or metformin, components of alogliptin and metformin HCl tablets, such as anaphylaxis, angioedema or severe cutaneous adverse reactions. (4)

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

- Lactic acidosis: See boxed warning. (5.1)
- Acute pancreatitis: There have been postmarketing reports of acute pancreatitis. If pancreatitis is suspected, promptly discontinue alogliptin and metformin HCl tablets. (5.2)
- Heart failure: Consider the risks and benefits of alogliptin and metformin HCl tablets prior to initiating treatment in patients at risk for heart failure. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of alogliptin and metformin HCl tablets. (5.3)
- Hypersensitivity: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with alogliptin such as anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. In such cases, promptly discontinue alogliptin and metformin HCl tablets, assess for other potential causes, institute appropriate monitoring and treatment and initiate alternative treatment for diabetes. (5.4)
- Hepatic effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt alogliptin and metformin HCl tablets and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart alogliptin and metformin HCl tablets if liver injury is confirmed and no alternative etiology can be found. (5.5)
- Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually. (5.6)
- Hypoglycemia: When used with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia. (5.7)
- Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.8)
- Bullous pemphigoid: There have been postmarketing reports 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 alogliptin and metformin HCl tablets. (5.9)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with alogliptin and metformin HCl tablets or any other antidiabetic drug. (5.10)

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

The most common adverse reactions (4% or greater incidence) are upper respiratory tract infection, nasopharyngitis, diarrhea, hypertension, headache, back pain and urinary tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Carbionic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.1)
- 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. (7.2)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.3)

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

- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy.(8.3)
- Pediatrics: Safety and effectiveness of alogliptin and metformin HCl tablets in patients below the age of 18 have not been established. (8.4)
- 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: 2/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally greater than 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 alogliptin and metformin HCl tablets and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

Alogliptin and metformin HCl 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 alogliptin and metformin is appropriate *[see Clinical Studies (14)]*.

Important Limitations of Use

Alogliptin and metformin HCl tablets are not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommendations for All Patients

- Healthcare providers should individualize the starting dose of alogliptin and metformin HCl tablets based on the patient's current regimen.
- Alogliptin and metformin HCl tablets should be taken twice daily with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin. Alogliptin and metformin HCl tablets must not be split before swallowing.
- Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg alogliptin and 2000 mg metformin HCl.
- The following doses are available:
  12.5 mg alogliptin and 500 mg metformin HCl
  12.5 mg alogliptin and 1000 mg metformin HCl

2.2 Recommendations for Use in Renal Impairment

Assess renal function prior to initiation of alogliptin and metformin HCl tablets and periodically thereafter.

Alogliptin and metformin HCl tablets is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m² *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Alogliptin and metformin HCl tablets are not recommended in patients with an eGFR between 30 and 60 mL/min/1.73 m² because these patients require a lower daily dosage of alogliptin than what is available in the fixed combination alogliptin and metformin HCl tablets product.

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue alogliptin and metformin HCl 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 m²; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart alogliptin and metformin HCl tablets if renal function is stable *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

- 12.5 mg/500 mg tablets are pale yellow, oblong, film-coated tablets with "12.5/500" debossed on one side and "322M" debossed on the other side
- 12.5 mg/1000 mg tablets are pale yellow, oblong, film-coated tablets with "12.5/1000" debossed on one side and "322M" debossed on the other side

4 CONTRAINDICATIONS

Alogliptin and metformin HCl tablets are contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m²) *[see Warnings and Precautions (5.1)]*.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to alogliptin or metformin, components of alogliptin and metformin HCl tablets, such as anaphylaxis, angioedema or severe cutaneous adverse reactions.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

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 (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate:pyruvate ratio; metformin plasma levels generally greater than 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 alogliptin and metformin HCl tablets. In alogliptin and metformin HCl 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/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue alogliptin and metformin HCl 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 postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*:

- Before initiating alogliptin and metformin HCl tablets, obtain an eGFR.
- Alogliptin and metformin HCl tablets is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² *[see Contraindications (4)]*.
- Alogliptin and metformin HCl tablets is not recommended in patients with an eGFR between 30 and 60 mL/min/1.73 m² because these patients require a lower dosage of alogliptin than what is available in the fixed combination alogliptin and metformin HCl tablets product.
- Obtain an eGFR at least annually in all patients taking alogliptin and metformin HCl tablets. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions

The concomitant use of alogliptin and metformin HCl 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 alogliptin and metformin HCl 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 m²; 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 alogliptin and metformin HCl 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. Alogliptin and metformin HCl tablets should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States

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

5.2 Pancreatitis

Acute pancreatitis has been reported in the postmarketing setting and in randomized clinical trials. In glycemic control trials in patients with type 2 diabetes, acute pancreatitis was reported in 6 (0.2%) patients treated with alogliptin 25 mg and 2 (<0.1%) patients treated with active comparators or placebo. In the EXAMINE trial (a cardiovascular outcomes trial of patients with type 2 diabetes and high cardiovascular (CV) risk), acute pancreatitis was reported in 10 (0.4%) patients treated with alogliptin and in 7 (0.3%) patients treated with placebo.

It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using alogliptin and metformin HCl tablets.

After initiation of alogliptin and metformin HCl tablets, patients should be observed for signs and symptoms of pancreatitis. If pancreatitis is suspected, alogliptin should promptly be discontinued and appropriate management should be initiated.

5.3 Heart Failure

In the EXAMINE trial which enrolled patients with type 2 diabetes and recent acute coronary syndrome, 106 (3.9%) of patients treated with alogliptin and 89 (3.3%) of patients treated with placebo were hospitalized for congestive heart failure.

Consider the risks and benefits of alogliptin and metformin HCl tablets prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Patients should be advised of the characteristic symptoms of heart failure and should be instructed to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of alogliptin and metformin HCl tablets.

5.4 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with alogliptin. These reactions include anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. If a serious hypersensitivity reaction is suspected, discontinue alogliptin and metformin HCl tablets, assess for other potential causes for the event and institute alternative treatment for diabetes *[see Adverse Reactions (6.3)]*. Use caution in patients with a history of angioedema with another dipeptidyl peptidase-4 (DPP-4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with alogliptin and metformin HCl tablets.

5.5 Hepatic Effects

There have been postmarketing reports of fatal and nonfatal hepatic failure in patients taking alogliptin, although some of the reports contain insufficient information necessary to establish the probable cause *[see Adverse Reactions (6.3)]*.

In glycemic control trials in patients with type 2 diabetes, serum alanine aminotransferase (ALT) elevations greater than three times the upper limit of normal (ULN) were reported in 1.3% of patients treated with alogliptin 25 mg and 1.7% of patients treated with active comparators or placebo. In the EXAMINE trial (a cardiovascular outcomes trial of patients with type 2 diabetes and high cardiovascular (CV) risk), increases in serum alanine aminotransferase three times the upper limit of the reference range occurred in 2.4% of patients treated with alogliptin and in 1.8% of patients treated with placebo.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have clinically significant liver enzyme elevations and if abnormal liver tests persist or worsen, alogliptin and metformin HCl tablets should be interrupted and investigation done to establish the probable cause. Alogliptin and metformin HCl tablets should not be restarted in these patients without another explanation for the liver test abnormalities.

5.6 Vitamin B_{12} Levels

In controlled, 29-week clinical trials of immediate-release metformin, 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 alogliptin and metformin HCl tablets, and any apparent abnormalities should be appropriately investigated and managed. 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 two to three year intervals may be useful.

5.7 Use with Medications Known to Cause Hypoglycemia

Alogliptin

Insulin and insulin secretagogues, such as sulfonylureas, are known to cause hypoglycemia. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with alogliptin and metformin HCl tablets.

Metformin Hydrochloride

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

5.8 Severe and Disabling Arthralgia

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

5.9 Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving alogliptin and metformin HCl tablets. If bullous pemphigoid is suspected, alogliptin and metformin HCl 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 alogliptin and metformin HCl tablets or any other antidiabetic drug.

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)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*
- Hepatic Effects *[see Warnings and Precautions (5.5)]*
- 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.

Alogliptin and Metformin Hydrochloride

Over 2700 patients with type 2 diabetes have received alogliptin coadministered with metformin in four large, randomized, double-blind controlled clinical trials. The mean exposure to alogliptin and metformin HCl tablets was 58 weeks, with more than 1400 subjects treated for more than one year. These included two 26 week placebo-controlled studies, one 52 week active control study and an interim analysis of a 104 week active-controlled study. In the alogliptin and metformin HCl tablets arm, the mean duration of diabetes was approximately six years, the mean body mass index (BMI) was 31 kg/m² (56% of patients had a BMI ≥30 kg/m²) and the mean age was 55 years (18% of patients ≥65 years of age).

In a pooled analysis of these four controlled clinical studies, the overall incidence of adverse reactions was 74% in patients treated with alogliptin and metformin HCl tablets compared to 75% treated with placebo. Overall discontinuation of therapy due to adverse reactions was 6.2% with alogliptin and metformin HCl tablets compared to 1.9% in placebo, 6.4% in metformin and 5.0% in alogliptin.

Adverse reactions reported in ≥4% of patients treated with alogliptin and metformin HCl tablets and more frequently than in patients who received alogliptin, metformin or placebo are summarized in Table 1.

Table 1. Adverse Reactions Reported in ≥4% of Patients Treated with Alogliptin and Metformin HCl Tablets and More Frequently Than in Patients Receiving Either Alogliptin, Metformin or Placebo

	Number of Patients (%)			
	Alogliptin and Metformin HCl Tablets*	Alogliptin†	Metformin‡	Placebo
	N=2794	N=222	N=1592	N=106
Upper respiratory tract infection	224 (8.0)	6 (2.7)	105 (6.6)	3 (2.8)
Nasopharyngitis	191 (6.8)	7 (3.2)	93 (5.8)	2 (1.9)
Diarrhea	155 (5.5)	4 (1.8)	105 (6.6)	3 (2.8)
Hypertension	154 (5.5)	5 (2.3)	96 (6.0)	6 (5.7)
Headache	149 (5.3)	11 (5.0)	74 (4.6)	3 (2.8)
Back pain	119 (4.3)	1 (0.5)	72 (4.5)	1 (0.9)
Urinary tract infection	116 (4.2)	4 (1.8)	59 (3.7)	2 (1.9)

*Alogliptin and metformin HCl tablets – includes data pooled for patients receiving alogliptin 25 and 12.5 mg combined with various dose of metformin
†Alogliptin – includes data pooled for patients receiving alogliptin 25 and 12.5 mg
‡Metformin – includes data pooled for patients receiving various doses of metformin

Hypoglycemia

In a 26 week, double-blind, placebo-controlled study of alogliptin in combination with metformin, the number of patients reporting hypoglycemia was 1.9% in the alogliptin 12.5 mg with metformin HCl 500 mg, 5.3% in the alogliptin 12.5 mg with metformin HCl 1000 mg, 1.8% in the metformin HCl 500 mg and 6.3% in the metformin HCl 1000 mg treatment groups.

In a 26 week placebo-controlled study of alogliptin 25 mg administered once daily as add-on to metformin regimen, the number of patients reporting hypoglycemic events was 0% in the alogliptin with metformin and 2.9% in the placebo treatment groups.

In a 52 week, active-controlled, double-blind study of alogliptin once daily as add-on therapy to the combination of pioglitazone 30 mg and metformin compared to the titration of pioglitazone 30 mg to 45 mg and metformin, the number of patients reporting hypoglycemia was 4.5% in the alogliptin 25 mg with pioglitazone 30 mg and metformin group versus 1.5% in the pioglitazone 45 mg with metformin group.

In an interim analysis conducted in a 104 week, double-blind, active-controlled study of alogliptin 25 mg in combination with metformin, the number of patients reporting hypoglycemia was 1.4% in the alogliptin 25 mg with metformin group versus 23.8% in the glipizide with metformin group.

Alogliptin

A total of 14,778 patients with type 2 diabetes participated in 14 randomized, double-blind, controlled clinical trials of whom 9052 subjects were treated with alogliptin, 3469 subjects were treated with placebo and 2257 were treated with an active comparator. The mean duration of diabetes was seven years, the mean body mass index (BMI) was 31 kg/m² (49% of patients had a BMI ≥30 kg/m²), and the mean age was 58 years (26% of patients ≥65 years of age). The mean exposure to alogliptin was 49 weeks with 3348 subjects treated for more than one year.

In a pooled analysis of these 14 controlled clinical trials, the overall incidence of adverse reactions was 73% in patients treated with alogliptin 25 mg compared to 75% with placebo and 70% with active comparator. Overall discontinuation of therapy due to adverse reactions was 6.8% with alogliptin 25 mg compared to 8.4% with placebo or 6.2% with active comparator.

Adverse reactions reported in ≥4% of patients treated with alogliptin 25 mg and more frequently than in patients who received placebo are summarized in Table 2.

Table 2. Adverse Reactions Reported in ≥4% Patients Treated with Alogliptin 25 mg and More Frequently Than in Patients Given Placebo in Pooled Studies

	Number of Patients (%)		
	Alogliptin 25 mg	Placebo	Active Comparator
	N=6447	N=3469	N=2257
Nasopharyngitis	309 (4.8)	152 (4.4)	113 (5.0)
Upper Respiratory Tract Infection	287 (4.5)	121 (3.5)	113 (5.0)
Headache	278 (4.3)	101 (2.9)	121 (5.4)

Hypoglycemia

Hypoglycemic events were documented based upon a blood glucose value and/or clinical signs and symptoms of hypoglycemia.

In the monotherapy study, the incidence of hypoglycemia was 1.5% in patients treated with alogliptin compared to 1.6% with placebo. The use of alogliptin as add-on therapy to glyburide or insulin did not increase the incidence of hypoglycemia compared to placebo. In a monotherapy study comparing alogliptin to a sulfonylurea in elderly patients, the incidence of hypoglycemia was 5.4% with alogliptin compared to 26% with glipizide.

In the EXAMINE trial, the incidence of investigator reported hypoglycemia was 6.7% in patients receiving alogliptin and 6.5% in patients receiving placebo. Serious adverse reactions of hypoglycemia were reported in 0.8% of patients treated with alogliptin and in 0.6% of patients treated with placebo.

Metformin Hydrochloride

Table 3. Most Common Adverse Reactions (≥5%) in a Placebo-Controlled Clinical Study of Metformin Monotherapy*

Adverse Reaction	Metformin Monotherapy (n=141)	Placebo (n=145)
	% of Patients	
Diarrhea	53.2	11.7
Nausea/vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal discomfort	6.4	4.8
Headache	5.7	4.8

*Reactions that were more common in metformin than placebo-treated patients

6.2 Laboratory Abnormalities

Alogliptin and Metformin Hydrochloride

No clinically meaningful differences were observed among treatment groups regarding hematology, serum chemistry or urinalysis results.

Metformin Hydrochloride

Metformin may lower serum vitamin B_{12} concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on alogliptin and metformin HCl tablets, and any apparent abnormalities should be appropriately investigated and managed *[see Warnings and Precautions (5.6)]*.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Alogliptin

Acute pancreatitis, hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria and severe cutaneous adverse reactions, including Stevens-Johnson syndrome, hepatic enzyme elevations, fulminant hepatic failure, severe and disabling arthralgia and bullous pemphigoid, diarrhea, constipation, nausea, and ileus *[see Warnings and Precautions (5.2, 5.4, 5.5, 5.8, 5.9)]*.

Metformin

Cholestatic, hepatocellular, and mixed hepatocellular liver injury.

7 DRUG INTERACTIONS

Alogliptin

Alogliptin is primarily renally excreted. Cytochrome (CYP) P450-related metabolism is negligible. No significant drug-drug interactions were observed with the CYP-substrates or inhibitors tested or with renally excreted drugs *[see Clinical Pharmacology (12.3)]*.

Metformin Hydrochloride

7.1 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce nonanion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with alogliptin and metformin HCl tablets may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.

7.2 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.

7.3 Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving alogliptin and metformin HCl tablets.

7.4 Insulin Secretagogues and Insulin

When used in an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia.

7.5 The Use of Metformin with Other Drugs

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs and isoniazid. When such drugs are administered to a patient receiving alogliptin and metformin HCl tablets, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving alogliptin and metformin HCl tablets, the patient should be observed closely for hypoglycemia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with alogliptin and metformin HCl tablets or alogliptin in pregnant women are not sufficient to inform 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]*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

Concomitant administration of alogliptin and metformin in pregnant rats during the period of organogenesis did not cause adverse developmental effects in offspring at maternal exposures up to 28 times and two times the 25 mg and 2000 mg clinical doses, respectively *[see Data]*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c > 7 and has been reported to be as high as 20-25% in women with HbA1c > 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 defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Data

Human Data

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

Animal Data

Alogliptin and Metformin

Concomitant administration of alogliptin and metformin in pregnant rats during the period of organogenesis did not cause adverse developmental effects in offspring at a dose of 100 mg/kg alogliptin and 150 mg/kg metformin, or approximately 28 and two times the clinical dose of alogliptin (25 mg) and metformin (2000 mg), respectively based on plasma drug exposure (AUC).

Alogliptin

Alogliptin administered to pregnant rabbits and rats during the period of organogenesis did not cause adverse developmental effects at doses of up to 200 mg/kg and 500 mg/kg, or 149 times and 180 times the 25 mg clinical dose, respectively, based on plasma drug exposure (AUC). Placental transfer of alogliptin into the fetus was observed following oral dosing to pregnant rats.

No adverse developmental outcomes were observed in offspring when alogliptin was administered to pregnant rats during gestation and lactation at doses up to 250 mg/kg (approximately 95 times the 25 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 two to six times a clinical dose of 2000 mg based on body surface area (mg/m²) for rats and rabbits, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of alogliptin and metformin or alogliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Alogliptin is present in rat milk. Limited published studies report that metformin is present in human milk *[see Data]*. However, there is insufficient information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for alogliptin and metformin HCl tablets and any potential adverse effects on the breastfed infant from alogliptin and metformin HCl tablets or from the underlying maternal condition.

Data

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 (based on AUC) ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

8.3 Females and Males of Reproductive Potential

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

8.4 Pediatric Use

Safety and effectiveness of alogliptin and metformin HCl tablets in pediatric patients have not been established.

8.5 Geriatric Use

Alogliptin and Metformin Hydrochloride

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

Of the total number of patients (N = 2095) in clinical safety and efficacy studies, 343 (16.4%) patients were 65 years and older and 37 (1.8%) patients were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients. While this and other reported clinical experiences have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be excluded.

Alogliptin

Of the total number of patients (N=9052) in clinical safety and efficacy studies treated with alogliptin, 2257 (24.9%) patients were 65 years and older and 386 (4.3%) patients were 75 years and older. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients.

Metformin Hydrochloride

Controlled studies of metformin did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

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 and 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

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Alogliptin and metformin HCl tablets is contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m² *[see Dosage and Administration (2.2), 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. Alogliptin and metformin HCl tablets are not recommended in patients with hepatic impairment *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

Alogliptin

The highest doses of alogliptin administered in clinical trials were single doses of 800 mg to healthy subjects and doses of 400 mg once daily for 14 days to patients with type 2 diabetes (equivalent to 32 times and 16 times the maximum recommended clinical dose of 25 mg, respectively). No serious adverse reactions were observed at these doses.

In the event of an overdose, it is reasonable to institute the necessary clinical monitoring and supportive therapy as dictated by the patient's clinical status. Per clinical judgment, it may be reasonable to initiate removal of unabsorbed material from the gastrointestinal tract.

Alogliptin is minimally dialyzable; over a three-hour hemodialysis session, approximately 7% of the drug was removed. Therefore, hemodialysis is unlikely to be beneficial in an overdose situation. It is not known if alogliptin is dialyzable by peritoneal dialysis.

Metformin Hydrochloride

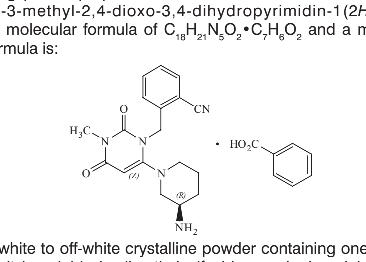
Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases *[see Warnings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

11 DESCRIPTION

Alogliptin and metformin HCl tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: alogliptin and metformin hydrochloride.

Alogliptin

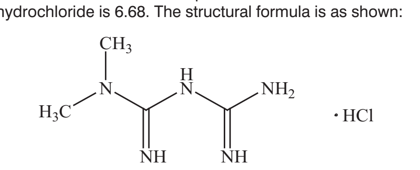
Alogliptin is a selective, orally bioavailable inhibitor of the enzymatic activity of dipeptidyl peptidase-4 (DPP-4). Chemically, alogliptin is prepared as a benzoate salt, which is identified as 2-({6-[(3*R*)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl)benzonitrile monobenzoate. It has a molecular formula of $C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$ and a molecular weight of 461.51 daltons; the structural formula is:



Alogliptin benzoate is a white to off-white crystalline powder containing one asymmetric carbon in the aminopiperidine moiety. It is soluble in dimethylsulfoxide, sparingly soluble in water and methanol, slightly soluble in ethanol and very slightly soluble in octanol and isopropyl acetate.

Metformin Hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:



Alogliptin and metformin HCl tablets are available as a tablet for oral administration containing 17 mg alogliptin benzoate equivalent to 12.5 mg alogliptin and:

- 500 mg metformin hydrochloride (12.5 mg/500 mg) or
- 1000 mg metformin hydrochloride (12.5 mg/1000 mg).

Alogliptin and metformin HCl tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, povidone, crospovidone, and magnesium stearate; the tablets are film-coated with hypromellose 2910, talc, titanium dioxide and ferric oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alogliptin and Metformin Hydrochloride

Alogliptin and metformin HCl tablets combine two antihyperglycemic agents with complementary and distinct mechanisms of action to improve glycemic control in patients with type 2 diabetes: alogliptin, a selective inhibitor of DPP-4, and metformin HCl, a member of the biguanide class.

Alogliptin

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 dipeptidyl peptidase-4 (DPP-4) 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. Alogliptin is a DPP-4 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. Alogliptin selectively binds to and inhibits DPP-4 but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Metformin Hydrochloride

Metformin is a biguanide that 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. Metformin does not produce hypoglycemia in patients with type 2 diabetes or in healthy subjects except in special circumstances *[see Warnings and Precautions (5.7)]* and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.

12.2 Pharmacodynamics

Alogliptin

Single-dose administration of alogliptin to healthy subjects resulted in a peak inhibition of DPP-4 within two to three hours after dosing. The peak inhibition of DPP-4 exceeded 93% across doses of 12.5 mg to 800 mg. Inhibition of DPP-4 remained above 80% at 24 hours for doses greater than or equal to 25 mg. Peak and total exposure over 24 hours to active GLP-1 were three- to four-fold greater with alogliptin (at doses of 25 to 200 mg) than placebo. In a 16 week, double-blind, placebo-controlled study, alogliptin 25 mg demonstrated decreases in postprandial glucagon while increasing postprandial active GLP-1 levels compared to placebo over an eight hour period following a standardized meal. It is unclear how these findings relate to changes in overall glycemic control in patients with type 2 diabetes mellitus. In this study, alogliptin 25 mg demonstrated decreases in two hour postprandial glucose compared to placebo (-30 mg/dL versus 17 mg/dL, respectively).

Multiple-dose administration of alogliptin to patients with type 2 diabetes also resulted in a peak inhibition of DPP-4 within one to two hours and exceeded 93% across all doses (25 mg, 100 mg and 400 mg) after a single dose and after 14 days of once daily dosing. At these doses of alogliptin, inhibition of DPP-4 remained above 81% at 24 hours after 14 days of dosing.

12.3 Pharmacokinetics

Absorption and Bioavailability

Alogliptin and Metformin Hydrochloride

In bioequivalence studies of alogliptin and metformin HCl tablets, the area under the plasma concentration curve (AUC) and maximum concentration (C_{max}) of both the alogliptin and the metformin component following a single dose of the combination tablet were bioequivalent to the alogliptin 12.5 mg concomitantly administered with metformin HCl 500 or 1000 mg tablets under fasted conditions in healthy subjects. Administration of alogliptin and metformin HCl tablets with food resulted in no change in total exposure (AUC) of alogliptin and metformin. Mean peak plasma concentrations of alogliptin and metformin were decreased by 13% and 28%, respectively, when administered with food. There was no change in time to peak plasma concentrations (T_{max}) for alogliptin under fed conditions, however, there was a delayed T_{max} for metformin of 1.5 hours. These changes are not likely to be clinically significant.

Alogliptin

The absolute bioavailability of alogliptin is approximately 100%. Administration of alogliptin with a high-fat meal results in no significant change in total and peak exposure to alogliptin. Alogliptin may therefore be administered with or without food.

Metformin Hydrochloride

The absolute bioavailability of metformin following administration of a 500 mg metformin HCl tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin HCl tablets 500 mg to 1500 mg and 850 mg to 2550 mg indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin HCl with food compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Alogliptin

Following a single, 12.5 mg intravenous infusion of alogliptin to healthy subjects, the volume of distribution during the terminal phase was 417 L, indicating that the drug is well distributed into tissues.

Alogliptin is 20% bound to plasma proteins.

Metformin Hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate release metformin HCl tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally less than 1 mcg/mL. During controlled clinical trials, which served as the basis for approval for metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

Alogliptin

Alogliptin does not undergo extensive metabolism and 60% to 71% of the dose is excreted as unchanged drug in the urine.

Two minor metabolites were detected following administration of an oral dose of [^{14}C] alogliptin, *N*-demethylated, M-I (less than 1% of the parent compound), and *N*-acetylated alogliptin, M-II (less than 6% of the parent compound). M-I is an active metabolite and is an inhibitor of DPP-4 similar to the parent molecule; M-II does not display any inhibitory activity toward DPP-4 or other DPP-related enzymes. *In vitro* data indicate that CYP2D6 and CYP3A4 contribute to the limited metabolism of alogliptin.

Alogliptin exists predominantly as the (*R*)-enantiomer (more than 99%) and undergoes little or no chiral conversion *in vivo* to the (*S*)-enantiomer. The (*S*)-enantiomer is not detectable at the 25 mg dose.

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.

Excretion and Elimination

Alogliptin

The primary route of elimination of [^{14}C] alogliptin-derived radioactivity occurs via renal excretion (76%) with 13% recovered in the feces, achieving a total recovery of 89% of the administered radioactive dose. The renal clearance of alogliptin (9.6 L/hr) indicates some active renal tubular secretion and systemic clearance was 14.0 L/hr.

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.

Special Populations

Renal Impairment

Metformin Hydrochloride

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

Hepatic Impairment

Alogliptin

Total exposure to alogliptin was approximately 10% lower and peak exposure was approximately 8% lower in patients with moderate hepatic impairment (Child-Pugh Grade B) compared to healthy subjects. The magnitude of these reductions is not considered to be clinically meaningful. Patients with severe hepatic impairment (Child-Pugh Grade C) have not been studied.

Metformin Hydrochloride

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

Gender

Alogliptin

No dose adjustment is necessary based on gender. Gender did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Metformin Hydrochloride

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

Geriatric

Due to declining renal function in the elderly, measurement of creatinine clearance should be obtained prior to initiation of therapy.

Alogliptin

No dose adjustment is necessary based on age. Age did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

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.

Pediatrics

Studies characterizing the pharmacokinetics of alogliptin in pediatric patients have not been performed.

Race

Alogliptin

No dose adjustment of alogliptin is necessary based on race. Race (white, black and Asian) did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

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 Interactions

Alogliptin and Metformin Hydrochloride

Administration of alogliptin 100 mg once daily with metformin HCl 1000 mg twice daily for six days had no meaningful effect on the pharmacokinetics of alogliptin or metformin.

Specific pharmacokinetic drug interaction studies with alogliptin and metformin HCl tablets have not been performed, although such studies have been conducted with the individual components of alogliptin and metformin HCl tablets (alogliptin and metformin).

Alogliptin

***In Vitro* Assessment of Drug Interactions**

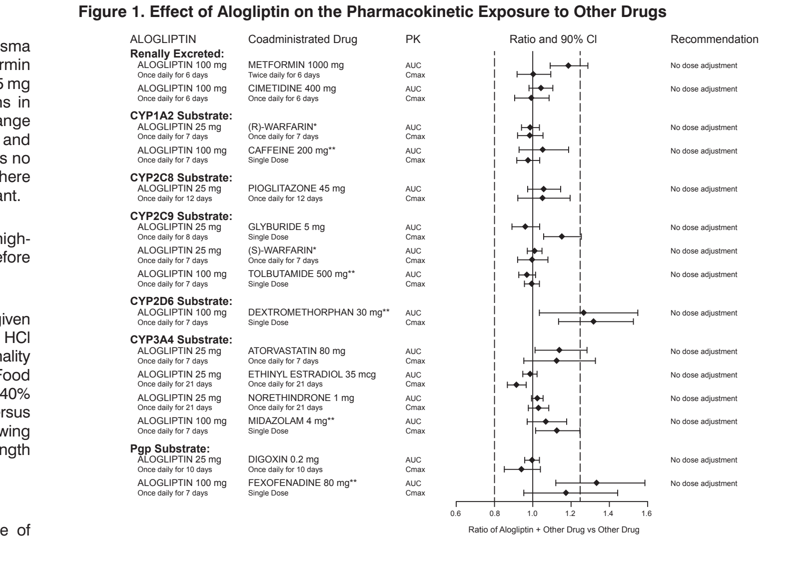
In vitro studies indicate that alogliptin is neither an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4, nor an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP2D6 at clinically relevant concentrations.

***In Vivo* Assessment of Drug Interactions**

Effects of Alogliptin on the Pharmacokinetics of Other Drugs

In clinical studies, alogliptin did not meaningfully increase the systemic exposure to the following drugs that are metabolized by CYP isozymes or excreted unchanged in urine *(Figure 1)*. No dose adjustment of alogliptin is recommended based on results of the described pharmacokinetic studies.

Figure 1. Effect of Alogliptin on the Pharmacokinetic Exposure to Other Drugs

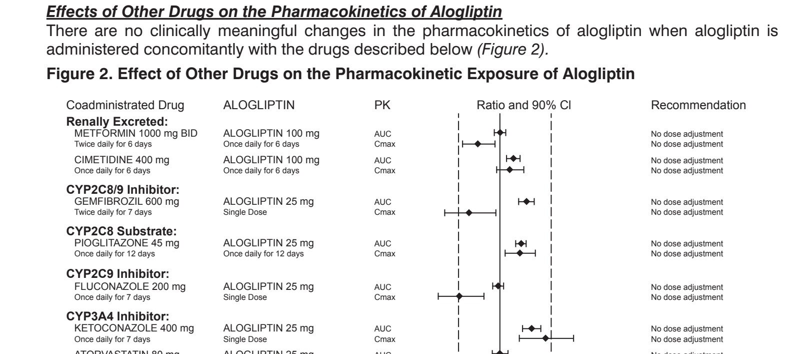


*Warfarin was given once daily at a stable dose in the range of 1 mg to 10 mg. Alogliptin had no significant effect on the prothrombin time (PT) or International Normalized Ratio (INR).
**Caffeine (1A2 substrate), tolbutamide (2C9 substrate), dextromethorphan (2D6 substrate), midazolam (3A4 substrate) and fexofenadine (P-gp substrate) were administered as a cocktail.

Effects of Other Drugs on the Pharmacokinetics of Alogliptin

There are no clinically meaningful changes in the pharmacokinetics of alogliptin when alogliptin is administered concomitantly with the drugs described below *(Figure 2)*.

Figure 2. Effect of Other Drugs on the Pharmacokinetic Exposure of Alogliptin



Metformin Hydrochloride

Pharmacokinetic drug interaction studies have been performed on metformin *(Tables 4 and 5)*.

Table 4. Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	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	500 mg‡	0.98§	0.99§
Furosemide	40 mg	850 mg	1.09§	1.22§
Nifedipine	10 mg	850 mg	1.16	1.21
Propranolol	40 mg	850 mg	0.90	0.94
Ibuprofen	400 mg	850 mg	1.05§	1.07§
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin *[see Warnings and Precautions (5) and Drug Interactions (7)]*.				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis *[see Warnings and Precautions (5) and Drug Interactions (7)]*				
Topiramate	100 mg¶	500 mg¶	1.25¶	1.17

*All metformin and coadministered drugs were given as single doses
†AUC = $AUC_{0-\infty}$
‡metformin hydrochloride extended-release tablets 500 mg
§Ratio of arithmetic means
¶At steady-state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC_{0-12h}

Table 5. Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	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	500 mg‡	0.78§	0.63§
Furosemide	40 mg	850 mg	0.87§	0.69§
Nifedipine	10 mg	850 mg	1.10‡	1.08
Propranolol	40 mg	850 mg	1.01‡	0.94
Ibuprofen	400 mg	850 mg	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	0.95‡	1.01

*All metformin and coadministered drugs were given as single doses
†AUC = $AUC_{0-\infty}$
‡AUC_{0-24} hr reported
§Ratio of arithmetic means, p-value of difference <0.05
¶Ratio of arithmetic means

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Alogliptin and Metformin Hydrochloride

No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with alogliptin and metformin HCl tablets. The following data are based on findings in studies performed with alogliptin or metformin individually.

Alogliptin

Rats were administered oral doses of 75, 400 and 800 mg/kg alogliptin for two years. No drug-related tumors were observed up to 75 mg/kg or approximately 32 times the maximum recommended clinical dose of 25 mg, based on area under the plasma concentration curve (AUC) exposure. At higher doses (approximately 308 times the maximum recommended clinical dose of 25 mg), a combination of thyroid C-cell adenomas and carcinomas increased in male but not female rats. No drug-related tumors were observed in mice after administration of 50, 150 or 300 mg/kg alogliptin for two years, or up to approximately 51 times the maximum recommended clinical dose of 25 mg, based on AUC exposure.

Alogliptin was not mutagenic or clastogenic, with and without metabolic activation, in the Ames test with *S. typhimurium* and *E. coli* or the cytogenetic assay in mouse lymphoma cells. Alogliptin was negative in the *in vivo* mouse micronucleus study.

In a fertility study in rats, alogliptin had no adverse effects on early embryonic development, mating or fertility, at doses up to 500 mg/kg, or approximately 172 times the clinical dose based on plasma drug exposure (AUC).

Metformin Hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg and 1500 mg/kg, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 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 an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg.

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

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

14 CLINICAL STUDIES

The coadministration of alogliptin and metformin has been studied in patients with type 2 diabetes inadequately controlled on either diet and exercise alone, on metformin alone or metformin in combination with a thiazolidinedione.

There have been no clinical efficacy studies conducted with alogliptin and metformin HCl tablets; however, bioequivalence of alogliptin and metformin HCl tablets with coadministered alogliptin and metformin tablets was demonstrated, and efficacy of the combination of alogliptin and metformin has been demonstrated in three Phase 3 efficacy studies.

A total of 2095 patients with type 2 diabetes were randomized in three double-blind, placebo- or active-controlled clinical safety and efficacy studies conducted to evaluate the effects of alogliptin and metformin HCl tablets on glycemic control. The racial distribution of patients exposed to study medication was 69.2% white, 16.3% Asian, 6.5% black and 8.0% other racial groups. The ethnic distribution was 24.3% Hispanic. Patients had an overall mean age of approximately 54.4 years (range 22 to 80 years). In patients with type 2 diabetes, treatment with alogliptin and metformin HCl tablets produced clinically meaningful and statistically significant improvements in A1C versus comparator. As is typical for trials of agents to treat type 2 diabetes, the mean reduction in hemoglobin A1c (A1C) with alogliptin and metformin HCl tablets appears to be related to the degree of A1C elevation at baseline.

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

In a 26 week, double-blind, placebo-controlled study, a total of 784 patients inadequately controlled on diet and exercise alone (mean baseline A1C = 8.4%) were randomized to one of seven treatment groups: placebo; metformin HCl 500 mg or metformin HCl 1000 mg twice daily, alogliptin 12.5 mg twice daily, or alogliptin 25 mg daily; alogliptin 12.5 mg in combination with metformin HCl 500 mg or metformin HCl 1000 mg twice daily. Both coadministration treatment arms (alogliptin 12.5 mg + metformin HCl 500 mg and alogliptin 12.5 mg + metformin HCl 1000 mg) resulted in significant improvements in A1C (*Figure 2*) and FPG when compared with their respective individual alogliptin and metformin component regimens (*Table 6*). Coadministration treatment arms demonstrated improvements in two-hour postprandial glucose (PPG) compared to alogliptin alone or metformin alone (*Table 6*). A total of 12% of patients receiving alogliptin 12.5 mg + metformin HCl 500 mg, 3% of patients receiving alogliptin 12.5 mg + metformin HCl 1000 mg, 17% of patients receiving alogliptin 12.5 mg, 23% of patients receiving metformin HCl 500 mg, 11% of patients receiving metformin HCl 1000 mg and 39% of patients receiving placebo required glycemic rescue.

Improvements in A1C were not affected by gender, age, race or baseline BMI. The mean decrease in body weight was similar between metformin alone and alogliptin when coadministered with metformin. Lipid effects were neutral.

Table 6. Glycemic Parameters at Week 26 for Alogliptin and Metformin Alone and in Combination in Patients with Type 2 Diabetes

	Placebo	Alogliptin 12.5 mg twice daily	Metformin HCl 500 mg twice daily	Metformin HCl 1000 mg twice daily	Alogliptin 12.5 mg + Metformin HCl 500 mg twice daily	Alogliptin 12.5 mg + Metformin HCl 1000 mg twice daily
A1C (%)*	**N=102**	**N=104**	**N=103**	**N=108**	**N=102**	**N=111**
Baseline (mean)	8.5	8.4	8.5	8.4	8.5	8.4
Change from baseline (adjusted mean†)	0.1	-0.6	-0.7	-1.1	-1.2	-1.6
Difference from metformin (adjusted mean† with 95% confidence interval)	-	-	-	-	-0.6‡ (-0.9, -0.3)	-0.4‡ (-0.7, -0.2)
Difference from alogliptin (adjusted mean† with 95% confidence interval)	-	-	-	-	-0.7‡ (-1.0, -0.4)	-1.0‡ (-1.3, -0.7)
% of Patients (n/N) achieving A1C <7%§	4% (4/102)	20% (21/104)	27% (28/103)	34% (37/108)	47%§ (48/102)	59%§ (66/111)
FPG (mg/dL)*	**N=105**	**N=106**	**N=106**	**N=110**	**N=106**	**N=112**
Baseline (mean)	187	177	180	181	176	185
Change from baseline (adjusted mean†)	12	-10	-12	-32	-32	-46
Difference from metformin (adjusted mean† with 95% confidence interval)	-	-	-	-	-20‡ (-33, -8)	-14‡ (-26, -2)
Difference from alogliptin (adjusted mean† with 95% confidence interval)	-	-	-	-	-22‡ (-35, -10)	-36‡ (-49, -24)
2-Hour PPG (mg/dL)¶	**N=26**	**N=34**	**N=28**	**N=37**	**N=31**	**N=37**
Baseline (mean)	263	272	247	266	261	268
Change from baseline (adjusted mean†)	-21	-43	-49	-54	-68	-86‡
Difference from metformin (adjusted mean† with 95% confidence interval)	-	-	-	-	-19 (-49, 11)	-32‡ (-58, -5)
Difference from alogliptin (adjusted mean† with 95% confidence interval)	-	-	-	-	-25 (-53, 3)	-43‡ (-70, -16)

*Intent-to-treat population using last observation on study prior to discontinuation of double-blind study medication or sulfonylurea rescue therapy for patients needing rescue

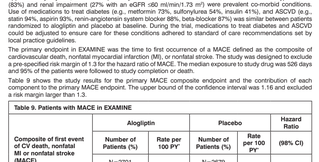
†Least squares means adjusted for treatment, geographic region and baseline value

‡p<0.05 when compared to metformin and alogliptin alone

§Compared using logistic regression

¶Intent-to-treat population using data available at Week 26

Figure 3. Change from Baseline A1C at Week 26 with Alogliptin and Metformin Alone and Alogliptin in Combination with Metformin



Intent-to-treat population using last observation on study prior to discontinuation of double-blind study medication or sulfonylurea rescue therapy for patients needing rescue.
*P<0.001 when compared to metformin and alogliptin alone.

Alogliptin and Metformin Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone

In a 26 week, double-blind, placebo-controlled study, a total of 527 patients already on metformin (mean baseline A1C = 8%) were randomized to receive alogliptin 12.5 mg, alogliptin 25 mg, or placebo once daily. Patients were maintained on a stable dose of metformin HCl (median daily dose = 1700 mg) during the treatment period. Alogliptin 25 mg in combination with metformin resulted in statistically significant improvements from baseline in A1C and FPG at Week 26, when compared to placebo (*Table 7*). A total of 8% of patients receiving alogliptin 25 mg and 24% of patients receiving placebo required glycemic rescue. Improvements in A1C were not affected by gender, age, race, baseline BMI or baseline metformin dose.

The mean decrease in body weight was similar between alogliptin 25 mg and placebo when given in combination with metformin. Lipid effects were also neutral.

Table 7. Glycemic Parameters at Week 26 in a Placebo-Controlled Study of Alogliptin as Add-on Therapy to Metformin*

	Alogliptin 25 mg + Metformin	Placebo + Metformin
A1C (%)	**N=203**	**N=103**
Baseline (mean)	7.9	8.0
Change from baseline (adjusted mean†)	-0.6	-0.1
Difference from placebo (adjusted mean† with 95% confidence interval)	-0.5‡ (-0.7, -0.3)	-
% of patients (n/N) achieving A1C <7%§	44% (92/207)‡	18% (19/104)
FPG (mg/dL)	**N=204**	**N=104**
Baseline (mean)	172	180
Change from baseline (adjusted mean†)	-17	0
Difference from placebo (adjusted mean† with 95% confidence interval)	-17‡ (-26, -9)	-

*Intent-to-treat population using last observation on study.
†Least squares means adjusted for treatment, baseline value, geographic region and baseline metformin dose.
‡p<0.001 compared to placebo.

Alogliptin Add-On Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Pioglitazone

In a 52 week, active-comparator study, a total of 803 patients inadequately controlled (mean baseline A1C = 8.2%) on a current regimen of pioglitazone 30 mg and metformin were randomized to either receive the addition of once-daily alogliptin 25 mg or the titration of pioglitazone 30 mg to 45 mg following a four-week single-blind, placebo run-in period. Patients were maintained on a stable dose of metformin HCl (median daily dose = 1700 mg). Patients who failed to meet prespecified hyperglycemic goals during the 52 week treatment period received glycemic rescue therapy.

In combination with pioglitazone and metformin, alogliptin 25 mg was shown to be statistically superior in lowering A1C and FPG compared with the titration of pioglitazone from 30 to 45 mg at Week 26 and at Week 52 (*Table 8*). A total of 11% of patients in the alogliptin 25 mg in combination with pioglitazone 30 mg and metformin treatment group and 22% of patients in the up titration of pioglitazone in combination with metformin treatment group required glycemic rescue. Improvements in A1C were not affected by gender, age, race or baseline BMI. The mean increase in body weight was similar in both treatment arms. Lipid effects were neutral.

Table 8. Glycemic Parameters at Week 52 in an Active-Controlled Study of Alogliptin as Add-On Combination Therapy to Metformin and Pioglitazone*

	Alogliptin 25 mg + Pioglitazone 30 mg + Metformin	Pioglitazone 45 mg + Metformin
A1C (%)	**N=397**	**N=394**
Baseline (mean)	8.2	8.1
Change from baseline (adjusted mean†)	-0.7	-0.3
Difference from pioglitazone 45 mg + metformin* (adjusted mean† with 95% confidence interval)	-0.4‡ (-0.5, -0.3)	
% of Patients (n/N) achieving A1C <7%	33% (134/404)‡	21% (85/399)
Fasting Plasma Glucose (mg/dL)†	**N=399**	**N=396**
Baseline (mean)	162	162
Change from baseline (adjusted mean†)	-15	-4
Difference from pioglitazone 45 mg + metformin (adjusted mean† with 95% confidence interval)	-11‡ (-16, -6)	

*Intent-to-treat population using last observation on study
†Least squares means adjusted for treatment, baseline value, geographic region and baseline metformin dose
‡Noninferior and statistically superior to metformin + pioglitazone at the 0.025 one-sided significance level
§p<0.001 compared to pioglitazone 45 mg + metformin

Cardiovascular Safety Trial

A randomized, double-blind, placebo-controlled cardiovascular outcomes trial (EXAMINE) was conducted to evaluate the cardiovascular risk of alogliptin. The trial compared the risk of major adverse cardiovascular events (MACE) between alogliptin (N=2701) and placebo (N=2679) when added to standard of care therapies for diabetes and atherosclerotic vascular disease (ASCVD). The trial was event driven and patients were followed until a sufficient number of primary outcome events accrued.

Eligible patients were adults with type 2 diabetes who had inadequate glycemic control at baseline (e.g., HbA1c >6.5%) and had been hospitalized for an acute coronary syndrome event (e.g., acute myocardial infarction or unstable angina requiring hospitalization) 15 to 90 days prior to randomization. The dose of alogliptin was based on estimated renal function at baseline per dosage and administration recommendations. The average time between an acute coronary syndrome event and randomization was approximately 48 days.

The mean age of the population was 61 years. Most patients were male (68%), Caucasian (73%), and were recruited from outside of the United States (86%). Asian and Black patients contributed 20% and 4% of the total population, respectively. At the time of randomization patients had a diagnosis of type 2 diabetes mellitus for approximately 9 years, 87% had a prior myocardial infarction and 14% were current smokers. Hypertension (92%) and renal impairment (47% with an eGFR <60 mL/min/1.73 m²) were prevalent co-morbid conditions. Use of medications to treat diabetes (e.g., metformin 73%, sulfonylurea 54%, insulin 41%), and ASCVD (e.g., statin 84%, aspirin 82%, renin-angiotensin system blocker 88%, beta-blocker 87%) was similar between patients randomized to alogliptin and placebo at baseline. During the trial, medications to treat diabetes and ASCVD could be adjusted to ensure care for these conditions adhered to standard of care recommendations set by local practice guidelines.

The primary endpoint in EXAMINE was the time to first occurrence of a MACE defined as the composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. The study was designed to exclude a pre-specified risk margin of 1.3 for the hazard ratio of MACE. The median exposure to study drug was 526 days and 95% of the patients were followed to study completion or death.

Table 9 shows the study results for the primary MACE composite endpoint and the contribution of each component to the composite MACE endpoint. The upper bound of the confidence interval was 1.16 and excluded a risk margin larger than 1.3.

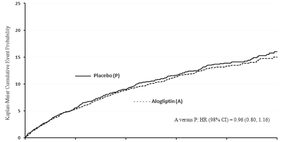
Table 9. Patients with MACE in EXAMINE

	Alogliptin		Placebo		Hazard Ratio
Composite of first event of CV death, nonfatal MI or nonfatal stroke (MACE)	**Number of Patients (%)** N=2701	**Rate per 100 PY***	**Number of Patients (%)** N=2679	**Rate per 100 PY***	**(98% CI)**
	305 (11.3)	7.6	316 (11.8)	7.9	0.96 (0.80, 1.16)
CV Death	89 (3.3)	2.2	111 (4.1)	2.8	
Non-fatal MI	187 (6.9)	4.6	173 (6.5)	4.3	
Non-fatal stroke	29 (1.1)	0.7	32 (1.2)	0.8	

*Patient Years (PY)

The Kaplan-Meier based cumulative event probability is presented in Figure 4 for the time to first occurrence of the primary MACE composite endpoint by treatment arm. The curves for placebo and alogliptin overlap throughout the duration of the study. The observed incidence of MACE was highest within the first 60 days after randomization in both treatment arms (14.8 MACE per 100 PY), decreased from day 60 to the end of the first year (8.4 per 100 PY) and was lowest after 1 year of follow-up (5.2 per 100 PY).

Figure 4. Observed Cumulative Rate of MACE in EXAMINE



The rate of all cause death was similar between treatment arms with 153 (3.6 per 100 PY) recorded among patients randomized to alogliptin and 173 (4.1 per 100 PY) among patients randomized to placebo. A total of 112 deaths (2.9 per 100 PY) among patients on alogliptin and 130 among patients on placebo (3.5 per 100 PY) were adjudicated as cardiovascular deaths.

16 HOW SUPPLIED/STORAGE AND HANDLING

Alogliptin and metformin HCl tablets are available in the following strengths and packages:

12.5 mg/500 mg tablet: pale yellow, oblong, film-coated tablets with "12.5/500" debossed on one side and "322M" debossed on the other side, available in:

NDC 45802-169-72 Bottles of 60 tablets

12.5 mg/1000 mg tablet: pale yellow, oblong, film-coated tablets with "12.5/1000" debossed on one side and "322M" debossed on the other side, available in:

NDC 45802-211-72 Bottles of 60 tablets

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep container tightly closed.

17 PATIENT COUNSELING INFORMATION

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

- Inform patients of the potential risks and benefits of alogliptin and metformin HCl tablets.
- The risks of lactic acidosis, 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 alogliptin and metformin HCl tablets immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of alogliptin and metformin HCl tablets, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.
- Patients should be informed that acute pancreatitis has been reported during use of alogliptin. Patients should 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 alogliptin and metformin HCl tablets and contact their physician if persistent severe abdominal pain occurs.
- Patients should be informed of the signs and symptoms of heart failure. Before initiating alogliptin and metformin HCl tablets, patients should be asked about a history of heart failure or of 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.
- Patients should be informed that allergic reactions have been reported during use of alogliptin and metformin. If symptoms of allergic reactions (including skin rash, hives and swelling of the face, lips, tongue and throat that may cause difficulty in breathing or swallowing) occur, patients should be instructed to discontinue alogliptin and metformin HCl tablets and seek medical advice promptly.
- Patients should be informed that postmarketing reports of liver injury, sometimes fatal, have been reported during use of alogliptin. If signs or symptoms of liver injury occur, patients should be instructed to discontinue alogliptin and metformin HCl tablets and seek medical advice promptly.
- Patients should be informed about the importance of regular testing of renal function and hematological parameters when receiving treatment with alogliptin and metformin HCl tablets.
- Instruct patients to inform their doctor that they are taking alogliptin and metformin HCl tablets prior to any surgical or radiological procedure, as temporary discontinuation of alogliptin and metformin HCl tablets may be required until renal function has been confirmed to be normal *[see Warnings and Precautions (5.1)]*.
- Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving alogliptin and metformin HCl tablets.
- Inform patients that hypoglycemia can occur, particularly when an insulin secretagogue or insulin is used in combination with alogliptin and metformin HCl tablets. Explain the risks, symptoms and appropriate management of hypoglycemia.
- 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.
- Inform patients that bullous pemphigoid may occur with the class of drugs. Instruct patients to seek medical advice if blisters or erosions occur *[see Warnings and Precautions (5.10)]*.
- Instruct patients to take alogliptin and metformin HCl tablets once-daily twice daily. Alogliptin and metformin HCl tablets should be taken with food. If a dose is missed, advise patients not to double their next dose.
- Patients should be informed that the tablets must never be split.
- Inform female patients that treatment with metformin may result in an unintended pregnancy in some premenopausal anovulatory females due to its effects on ovulation *[see Use in Specific Populations (8.3)]*.

Instruct patients to read the Medication Guide before starting alogliptin and metformin HCl tablets therapy and to reread each time the prescription is refilled. Instruct patients to inform their healthcare provider if an unusual symptom develops or if a symptom persists or worsens.

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MEDICATION GUIDE
Alogliptin and Metformin HCl Tablets

Read this Medication Guide carefully before you start taking alogliptin and metformin HCl tablets and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about alogliptin and metformin HCl tablets, ask your doctor or pharmacist.

What is the most important information I should know about alogliptin and metformin HCl tablets?

Alogliptin and metformin HCl tablets can cause serious side effects, including:

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

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 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 alogliptin and metformin HCl 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 listed above. You doctor may decide to stop alogliptin and metformin HCl tablets for a while if you have any of these things.

Alogliptin and metformin HCl tablets can have other serious side effects. See "What are the possible side effects of alogliptin and metformin HCl tablets?"

2. **Inflammation of the pancreas (pancreatitis).** Alogliptin, one of the medicines in alogliptin and metformin HCl tablets, may cause pancreatitis, which may be severe. Certain medical conditions make you more likely to get pancreatitis.

Before you start taking alogliptin and metformin HCl tablets:

Tell your doctor if you have ever had:

- pancreatitis
- kidney problems
- liver problems

Stop taking alogliptin and metformin HCl tablets and call your doctor 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:**

Before you start taking alogliptin and metformin HCl 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 lying down
- an unusually fast increase in weight
- swelling of feet, ankles, or legs

These may be symptoms of heart failure.

What are alogliptin and metformin HCl tablets?

- Alogliptin and metformin HCl tablets contain 2 prescription diabetes medicines, alogliptin (NESINA) and metformin hydrochloride.
- Alogliptin and metformin HCl tablets are a prescription medicine used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.
- Alogliptin and metformin HCl tablets are not for people with type 1 diabetes.
- Alogliptin and metformin HCl tablets are not for people with diabetic ketoacidosis (increased ketones in blood or urine).

It is not known if alogliptin and metformin HCl tablets are safe and effective in children under the age of 18.

Who should not take alogliptin and metformin HCl tablets?

Do not take alogliptin and metformin HCl tablets if you:

- have severe kidney problems
- have a condition called metabolic acidosis or have had diabetic ketoacidosis (increased ketones in your blood or urine)
- are going to get an injection of dye or contrast agents for an x-ray procedure, alogliptin and metformin HCl tablets may need to be stopped for a short time. Talk to your doctor about when you should stop alogliptin and metformin HCl tablets and when you should start alogliptin and metformin HCl tablets again
- are allergic to alogliptin or metformin or any of the ingredients in alogliptin and metformin HCl tablets or have had a serious allergic (hypersensitivity) reaction to alogliptin or metformin. See the end of this Medication Guide for a complete list of the ingredients in alogliptin and metformin HCl tablets

Symptoms of a serious allergic reaction to alogliptin and metformin HCl 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 any of these symptoms, stop taking alogliptin and metformin HCl tablets and contact your doctor or go to the nearest hospital emergency room right away.

What should I tell my doctor before and during treatment with alogliptin and metformin HCl tablets?

Before you take alogliptin and metformin HCl tablets, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis)
- have severe kidney or liver problems
- have heart problems, including congestive heart failure
- are going to get an injection of dye or contrast agents for an x-ray procedure, alogliptin and metformin HCl tablets may need to be stopped for a short time. Talk to your doctor about when you should stop alogliptin and metformin HCl tablets and when you should start alogliptin and metformin HCl tablets again
- drink alcohol very often or drink a lot of alcohol in short-term "binge" drinking
- have other medical conditions
- are pregnant or plan to become pregnant. It is not known if alogliptin and metformin HCl tablets will harm your unborn baby. Talk with your doctor about the best way to control your blood sugar while you are pregnant or if you plan to become pregnant
- are breastfeeding or plan to breastfeed. It is not known whether alogliptin and metformin pass into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking alogliptin and metformin HCl tablets

Tell your doctor 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 and show it to your doctor and pharmacist before you start any new medicine.

Alogliptin and metformin HCl tablets may affect the way other medicines work, and other medicines may affect how alogliptin and metformin HCl tablets work. Contact your doctor before you start or stop other types of medicines.

How should I take alogliptin and metformin HCl tablets?

- Take alogliptin and metformin HCl tablets exactly as your doctor tells you to take it.
- Take alogliptin and metformin HCl tablets 2 times each day.
- Take alogliptin and metformin HCl tablets with food to lower your chances of having an upset stomach.
- Do not break or cut alogliptin and metformin HCl tablets before swallowing.
- Your doctor may need to change your dose of alogliptin and metformin HCl tablets to control your blood glucose. Do not change your dose unless told to do so by your doctor.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose, and take the next dose at your regular time. Do not take 2 doses of alogliptin and metformin HCl tablets at the same time.
- If you take too many alogliptin and metformin HCl tablets, call your doctor or go to the nearest hospital emergency room right away.
- If your body is under stress, such as from fever, infection, accident or surgery, the dose of your diabetes medicines may need to be changed. Call your doctor right away.
- Stay on your diet and exercise programs and check your blood sugar as your doctor tells you to.
- Your doctor may do certain blood tests before you start alogliptin and metformin HCl tablets and during treatment as needed. Your doctor may ask you to stop taking alogliptin and metformin HCl tablets based on the results of your blood tests due to how well your kidneys are working.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.

What are the possible side effects of alogliptin and metformin HCl tablets?

Alogliptin and metformin HCl tablets can cause serious side effects, including:

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

  If you have these symptoms, stop taking alogliptin and metformin HCl tablets and contact your doctor right away.
- **Liver problems.** Call your doctor right away if you have unexplained symptoms, such as:
  - nausea or vomiting
  - stomach pain
  - unusual or unexplained tiredness
  - loss of appetite
  - dark urine
  - yellowing of your skin or the whites of your eyes
- **Low blood sugar (hypoglycemia).** If you take alogliptin and metformin HCl tablets with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take alogliptin and metformin HCl tablets. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, and then call your doctor. Signs and symptoms of low blood sugar may include:
  - shaking or feeling jittery
  - fast heartbeat
  - hunger
  - change in mood
  - dizziness
  - sweating
  - change in vision
  - headache
  - confusion
- **Joint pain.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in alogliptin and metformin HCl tablets, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in alogliptin and metformin HCl tablets, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your doctor right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your doctor may tell you to stop taking alogliptin and metformin HCl tablets.

The most common side effects of alogliptin and metformin HCl tablets include:

- cold-like symptoms (upper respiratory tract infection)
- stuffy or runny nose and sore throat
- diarrhea
- increase in blood pressure
- headache
- back pain
- urinary tract infection

Taking alogliptin and metformin HCl tablets with food can help lessen the common stomach side effects of metformin that usually happen at the beginning of treatment. If you have unexplained stomach problems, tell your doctor. Stomach problems that start later, during treatment, may be a sign of something more serious.

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

These are not all the possible side effects of alogliptin and metformin HCl tablets. For more information, ask your doctor or pharmacist.

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

How should I store alogliptin and metformin HCl tablets?

- Store alogliptin and metformin HCl tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the container of alogliptin and metformin HCl tablets tightly closed.

Keep alogliptin and metformin HCl tablets and all medicines out of the reach of children.

General information about the safe and effective use of alogliptin and metformin HCl tablets

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not take alogliptin and metformin HCl tablets for a condition for which it was not prescribed. Do not give alogliptin and metformin HCl tablets to other people, even if they have the same symptoms you have. They may harm them.

This Medication Guide summarizes the most important information about alogliptin and metformin HCl tablets. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for information about alogliptin and metformin HCl tablets that is written for health professionals.

For more information go to www.perrigo.com or call 1-877-TAKEDA-7 (1-877-825-3327).

What are the ingredients in alogliptin and metformin HCl tablets?

Active ingredients: alogliptin and metformin hydrochloride

Inactive ingredients: mannitol, microcrystalline cellulose, povidone, crospovidone and magnesium stearate; the tablets are film-coated with hypromellose 2910, talc, titanium dioxide and ferric oxide yellow.

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

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