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

KAZANO (alogliptin and metformin hydrochloride) 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 bradyarrhythmia's. 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, hepatic impairment, and mitochondrial diseases. 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 KAZANO and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

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

Boxed Warning.....08/2026
Warnings and Precautions, Lactic Acidosis (5.1).....08/2026

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

KAZANO is a combination of alogliptin, a dipeptidyl-peptidase-4 (DPP-4) inhibitor and metformin hydrochloride (HCl), a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of Use: Should not be used in patients with type 1 diabetes mellitus. (1)

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

- Individualize the starting dosage based on the patient's current regimen. (2.1)
- Given orally twice daily with food. (2.1)
- Adjust the dosage based on effectiveness and tolerability while not exceeding the maximum recommended daily dosage 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 m^2.
- KAZANO 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 m^2. (4)
- Metabolic acidosis including diabetic ketoacidosis. (4)
- History of serious hypersensitivity to alogliptin or metformin, components of KAZANO or any of the excipients. (4)

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

- Lactic Acidosis: See boxed warning. (5.1)
- Pancreatitis: There have been postmarketing reports of acute pancreatitis. If pancreatitis is suspected, promptly discontinue KAZANO. (5.2)
- Heart Failure: Consider the risks and benefits of KAZANO 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 KAZANO. (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. If hypersensitivity reactions occur, discontinue KAZANO, treat promptly, and monitor until signs and symptoms resolve. (5.4)
- Hepatic Effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt KAZANO and assess patient for probable cause, then treat cause, if possible, to resolution or stabilization. Do not restart KAZANO 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. Measure hematologic parameters annually and B_{12} at 2-to-3-year intervals and manage any abnormalities. (5.6)
- Hypoglycemia: Consider lowering the dosage of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating KAZANO. (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 KAZANO. (5.9)

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

Most common adverse reactions (incidence ≥4%) 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 America, Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7)
- 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)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7)

---------- 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 KAZANO in pediatric patients 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: 08/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LACTIC ACIDOSIS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

2.2 Recommendations for Use in Renal Impairment

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

5.2 Pancreatitis

5.3 Heart Failure

5.4 Hypersensitivity Reactions

5.5 Hepatic Effects

5.6 Vitamin B_{12} Deficiency

5.7 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues

5.8 Severe and Disabling Arthralgia

5.9 Bullous Pemphigoid

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials in Adults with Type 2 Diabetes Mellitus

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

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

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

14.5 Cardiovascular Safety Trial

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* 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 bradyarrhythmia's. 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, hepatic impairment, and mitochondrial diseases [see Warnings and Precautions (5.1)].

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), Use in Specific Populations (8.6, 8.7)].

If metformin-associated lactic acidosis is suspected, immediately discontinue KAZANO® and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

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

Limitations of Use

KAZANO is not recommended for use in patients with type 1 diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- Individualize the starting dosage of KAZANO based on the patient's current regimen.
- KAZANO should be taken orally twice daily with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin. Do not split tablets.
- Adjust the dosage based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg alogliptin and 2000 mg metformin hydrochloride (HCl).

2.2 Recommendations for Use in Renal Impairment

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

KAZANO is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 *[see Contraindications (4), Warnings and Precautions (5.1)]*.

KAZANO is not recommended in patients with an eGFR between 30 and 59 mL/min/1.73 m^2 because these patients require a lower daily dosage of alogliptin than what is available in the fixed combination KAZANO product.

Kazano requires no dose adjustment in patients with an eGFR of 60 mL/min/1.73 m^2 or greater.

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue KAZANO at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of 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 KAZANO 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

KAZANO is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) *[see Warnings and Precautions (5.1)]*.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis with or without coma.
- History of serious hypersensitivity reaction to alogliptin or metformin or any of the excipients in KAZANO, such as anaphylaxis, angioedema and severe cutaneous adverse reactions *[see Warnings and Precautions (5.4), Adverse Reactions (6.2)].*

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 KAZANO. In KAZANO-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin HCl 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 KAZANO 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 KAZANO, obtain an eGFR.
- KAZANO is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see*

Contraindications (4)].

- KAZANO is not recommended in patients with an eGFR between 30 and 60 mL/min/1.73 m^2 because these patients require a lower dosage of alogliptin than what is available in the fixed combination KAZANO product.
- Obtain an eGFR at least annually in all patients taking KAZANO. 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 KAZANO 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 KAZANO at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart KAZANO if renal function is stable.

Surgery and Other Procedures

Withholding food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. KAZANO 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 KAZANO.

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 KAZANO.

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 KAZANO in patients with clinical or laboratory evidence of hepatic disease.

Mitochondrial Diseases

Metformin may increase the risk of lactic acidosis in patients with mitochondrial diseases such as mitochondrial encephalomyopathy with lactic acidosis, and stroke-like episodes (MELAS) syndrome and maternally inherited diabetes and deafness (MIDD). KAZANO is not recommended in patients with mitochondrial diseases such as MELAS syndrome and MIDD.

If a patient taking KAZANO develops elevated lactic acid levels (with or without accompanying neurologic signs and symptoms), discontinue KAZANO. Depending on the clinical context, consider

evaluating the patient for MELAS, MIDD, or other mitochondrial 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 mellitus, 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 mellitus 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 KAZANO.

After initiation of KAZANO, 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 mellitus 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 KAZANO 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 KAZANO.

5.4 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with alogliptin *[see Adverse Reactions (6.2)]*. These reactions include anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. If a serious hypersensitivity reaction is suspected, discontinue KAZANO, assess for other potential causes for the event and institute alternative treatment for diabetes mellitus. 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 KAZANO.

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 (6.2)]*.

In glycemic control trials in patients with type 2 diabetes mellitus, 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 mellitus 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, KAZANO should be interrupted and investigation done to establish the probable cause.

KAZANO should not be restarted in these patients without another explanation for the liver test abnormalities.

5.6 Vitamin B_{12} Deficiency

In metformin clinical trials of 29 week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. Measure hematologic parameters on an annual basis and vitamin B_{12} at 2 to 3 year intervals in patients on KAZANO and manage any abnormalities *[see Adverse Reactions (6.1)]*.

5.7 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues

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

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 KAZANO. If bullous pemphigoid is suspected, KAZANO should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

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 HCl

Over 2,700 patients with type 2 diabetes mellitus have received alogliptin coadministered with metformin in four large, randomized, double-blind controlled clinical trials. The racial distribution of patients exposed to trial medication was 65% White, 20% Asian, 7% Black or African American, 4% American Indian or

Alaska Native, 0% Native Hawaiian/Other Pacific Islander and 4% Multiracial or other racial groups. The ethnic distribution was 23% Hispanic or Latino and 77% was not Hispanic or Latino. The mean exposure to alogliptin coadministered with metformin was 58 weeks, with more than 1,400 subjects treated for more than one year. These included two 26 week placebo-controlled trials, one 52 week active control trial and an interim analysis of a 104 week active-controlled trial. In the alogliptin co-administered with metformin HCl arm, the mean duration of diabetes mellitus was approximately six years, the mean body mass index (BMI) was 31 kg/m^2 (56% of patients had a BMI ≥30 kg/m^2) 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 co-administered with metformin HCl compared to 75% treated with placebo. Overall discontinuation of therapy due to adverse reactions was 6.2% with alogliptin co-administered with metformin HCl 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 co-administered with metformin HCl 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 Adults with Type 2 Diabetes Mellitus Treated with Alogliptin Co-administered with Metformin HCl and More Frequently Than in Patients Receiving Either Alogliptin, Metformin or Placebo**

	Number of Patients (%)			
	Alogliptin and Metformin*	**Alogliptin†**	**Metformin‡**	**Placebo**
	N=2794	**N=222**	**N=1592**	**N=106**
Upper respiratory tract infection	224 (8)	6 (3)	105 (7)	3 (3)
Nasopharyngitis	191 (7)	7 (3)	93 (6)	2 (2)
Diarrhea	155 (6)	4 (2)	105 (7)	3 (3)
Hypertension	154 (6)	5 (2)	96 (6)	6 (6)
Headache	149 (5)	11 (5)	74 (5)	3 (3)
Back pain	119 (4)	1 (1)	72 (5)	1 (1)
Urinary tract infection	116 (4)	4 (2)	59 (4)	2 (2)

* Alogliptin and metformin – includes data pooled for patients receiving alogliptin 25 and 12.5 mg combined with various doses 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

Alogliptin

A total of 14,778 patients with type 2 diabetes mellitus participated in 14 randomized, double-blind, controlled clinical trials of whom 9,052 subjects were treated with alogliptin, 3,469 subjects were treated with placebo and 2,257 were treated with an active comparator. The racial distribution of patients exposed to trial medication was 71% White, 17% Asian, 6% Black or African American, 2% American Indian or Alaska Native, 0% Native Hawaiian/Other Pacific Islander and 5% Multiracial or other racial groups. The ethnic distribution was 30% Hispanic or Latino and 70% was not Hispanic or Latino. The mean duration of diabetes mellitus was seven years, the mean body mass index (BMI) was 31 kg/m^2 (49% of patients had a BMI ≥30 kg/m^2), and the mean age was 58 years (26% of patients ≥65 years of age). The mean exposure to alogliptin was 49 weeks with 3,348 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 (5)	152 (4)	113 (5)
Upper Respiratory Tract Infection	287 (5)	121 (4)	113 (5)
Headache	278 (4)	101 (3)	121 (5)

Hypoglycemia

Alogliptin and Metformin HCl

In a 26 week, double-blind, placebo-controlled trial 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 trial 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 co-administered with metformin HCl and 2.9% in the placebo treatment groups.

In a 52 week, active-controlled, double-blind trial 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 trial 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

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

In the monotherapy trial, 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 trial 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 HCl

Table 3:**Most Common Adverse Reactions (≥5%) in a Placebo-Controlled Clinical Trial 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

Laboratory Abnormalities

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

Metformin HCl
In metformin clinical trials of 29 week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of patients.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of alogliptin and metformin HCl. 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
Gastrointestinal Disorders: acute pancreatitis, diarrhea, constipation, nausea, ileus

Hepatobiliary Disorders: fulminant hepatic failure

Immune System Disorders: hypersensitivity reactions including anaphylaxis

Investigations: hepatic enzyme elevations

Musculoskeletal and Connective Tissue Disorders: severe and disabling arthralgia, rhabdomyolysis

Renal and Urinary Disorders: tubulointerstitial nephritis

Skin and Subcutaneous Tissue Disorders: angioedema, rash, urticaria and severe cutaneous adverse reactions including Stevens-Johnson syndrome, bullous pemphigoid

Metformin
Hepatobiliary Disorders: Cholestatic, hepatocellular, mixed hepatocellular liver injury

7 DRUG INTERACTIONS

Metformin HCl

Carbonic Anhydrase Inhibitors	
Clinical Impact:	Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with KAZANO may increase the risk of lactic acidosis.
Intervention:	Consider more frequent monitoring of these patients.
Examples:	Topiramate, zonisamide, acetazolamide or dichlorphenamide
Drugs that Reduce Metformin Clearance	
Clinical Impact:	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) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)]*.
Intervention:	Consider the benefits and risks of concomitant use.
Examples:	Ranolazine, vandetanib, dolutegravir, and cimetidine
Alcohol	
Clinical Impact:	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention:	Warn patients against excessive alcohol intake while receiving KAZANO.
Insulin Secretagogues and Insulin	
Clinical Impact:	Coadministration of KAZANO with an insulin secretagogue (e.g., sulfonylurea) or with insulin may increase the risk of hypoglycemia.
Intervention:	Patients may require a lower dose of the insulin secretagogue or insulin.
Drugs Affecting Glycemic Control	
Clinical Impact:	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.
Intervention:	When such drugs are administered to a patient receiving KAZANO, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving KAZANO, the patient should be observed closely for hypoglycemia.
Examples:	Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs and isoniazid

Alogliptin

Cytochrome (CYP) P450, CYP-Substrates or Inhibitors	
Clinical Impact:	Insulin Secretagogues and Insulin Insulin and insulin secretagogues are known to cause hypoglycemia. Coadministration of KAZANO with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower dosages of the insulin secretagogue or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.7)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Human Data

Published data from postmarketing 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 HCl

Metformin HCl 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/m^2) for rats and rabbits, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of KAZANO 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 KAZANO and any potential adverse effects on the breastfed infant from KAZANO 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

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

Effectiveness of alogliptin was not demonstrated in a 52 week, randomized, double-blind, placebo-controlled trial (NCT02856113) in 151 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus.

8.5 Geriatric Use

Alogliptin and Metformin HCl

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

Of the total number of patients (N=2095) in clinical safety and efficacy trials, 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.

Alogliptin

Of the total number of patients (N=9052) in clinical safety and efficacy studies treated with alogliptin, 2,257 (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 HCl

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), 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. KAZANO is contraindicated in severe renal

impairment, patients with an eGFR below 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1), 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. KAZANO is not recommended in patients with hepatic impairment *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

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)]*.

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 is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

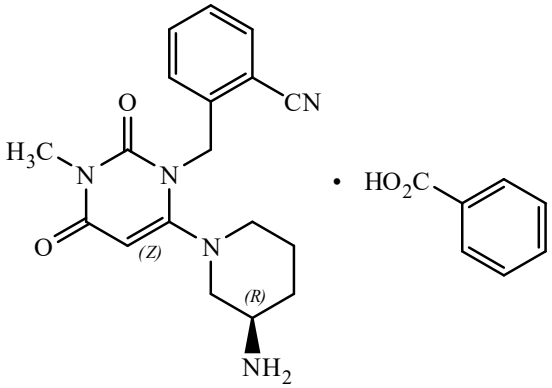
In the event of an overdose, contact the Poison Help Line, (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

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

Alogliptin

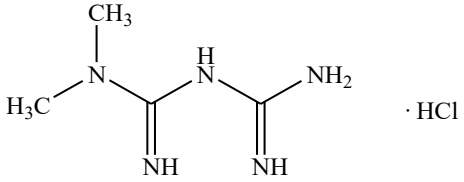
Alogliptin is a selective, orally bioavailable inhibitor of the enzymatic activity of DPP-4. Chemically, alogliptin is prepared as a benzoate salt, which is identified as 2-({6-[(3*R*)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl)benzonitrile monobenzoate. It has a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

Metformin HCl (*N,N*-dimethylimidodicarbonimidic diamide HCl) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin HCl is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin HCl 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 HCl is 6.68. The structural formula is as shown:



KAZANO is available as a tablet for oral administration containing 17 mg alogliptin benzoate equivalent to 12.5 mg alogliptin and:

- 500 mg metformin HCl which is equivalent to 389.93 mg metformin base (12.5 mg/500 mg) or
- 1000 mg metformin HCl which is equivalent to 779.86 mg metformin base (12.5 mg/1000 mg).

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alogliptin and Metformin HCl

KAZANO combines two antihyperglycemic agents with complementary and distinct mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: 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 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 mellitus, 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 HCl

Metformin is a biguanide that improves glucose tolerance in patients with type 2 diabetes mellitus, 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. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.

12.2 Pharmacodynamics

Dose-Response Relationships

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 mellitus 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.

Cardiac Electrophysiology

Alogliptin

In a randomized, placebo-controlled, four-arm, parallel-group study, 257 subjects were administered either alogliptin 50 mg, alogliptin 400 mg, moxifloxacin 400 mg or placebo once daily for a total of seven days. No increase in corrected QT (QTc) was observed with either dose of alogliptin. At the 400 mg dose, peak alogliptin plasma concentrations were 19-fold higher than the peak concentrations following the maximum recommended clinical dose of 25 mg.

12.3 Pharmacokinetics

Absorption

Alogliptin and Metformin HCl

There is no clinically meaningful difference in PK exposures (AUC and C_{max}) of alogliptin and metformin when taken a single dose of the combination tablet and individual alogliptin and metformin tablets taken concomitantly.

Alogliptin

After administration of single, oral doses up to 800 mg in healthy subjects, the peak plasma alogliptin concentration (median T_{max}) occurred one to two hours after dosing. The absolute bioavailability of alogliptin is approximately 100%.

Metformin HCl

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. The absolute bioavailability of metformin following administration of a 500 mg metformin HCl tablet given under fasting conditions is approximately 50% to 60%.

Effect of Food

Alogliptin and Metformin HCl

Administration of KAZANO 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

Administration of alogliptin with a high-fat meal results in no significant change in total and peak exposure to alogliptin.

Metformin HCl

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 HCl

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.

Elimination

Alogliptin

Alogliptin was eliminated with a mean terminal half-life ($t_{1/2}$) of approximately 21 hours. The renal clearance of alogliptin (9.6 L/hr) indicates some active renal tubular secretion and systemic clearance was 14.0 L/hr.

Metformin HCl

In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution. The plasma elimination half-life is approximately 6.2 hours. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin excretion.

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 HCl

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

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.

Metformin HCl

Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours.

Specific Populations

Geriatric Patients

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

Alogliptin

Age (18 to 80 years old) did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Metformin HCl
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.

Male and Female Patients
Alogliptin
Gender did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

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

Racial or Ethnic Groups
Alogliptin
Race (White, Black or African American and Asian) did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

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

Patients with Renal Impairment
Metformin HCl
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)]*.

Patients with 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.

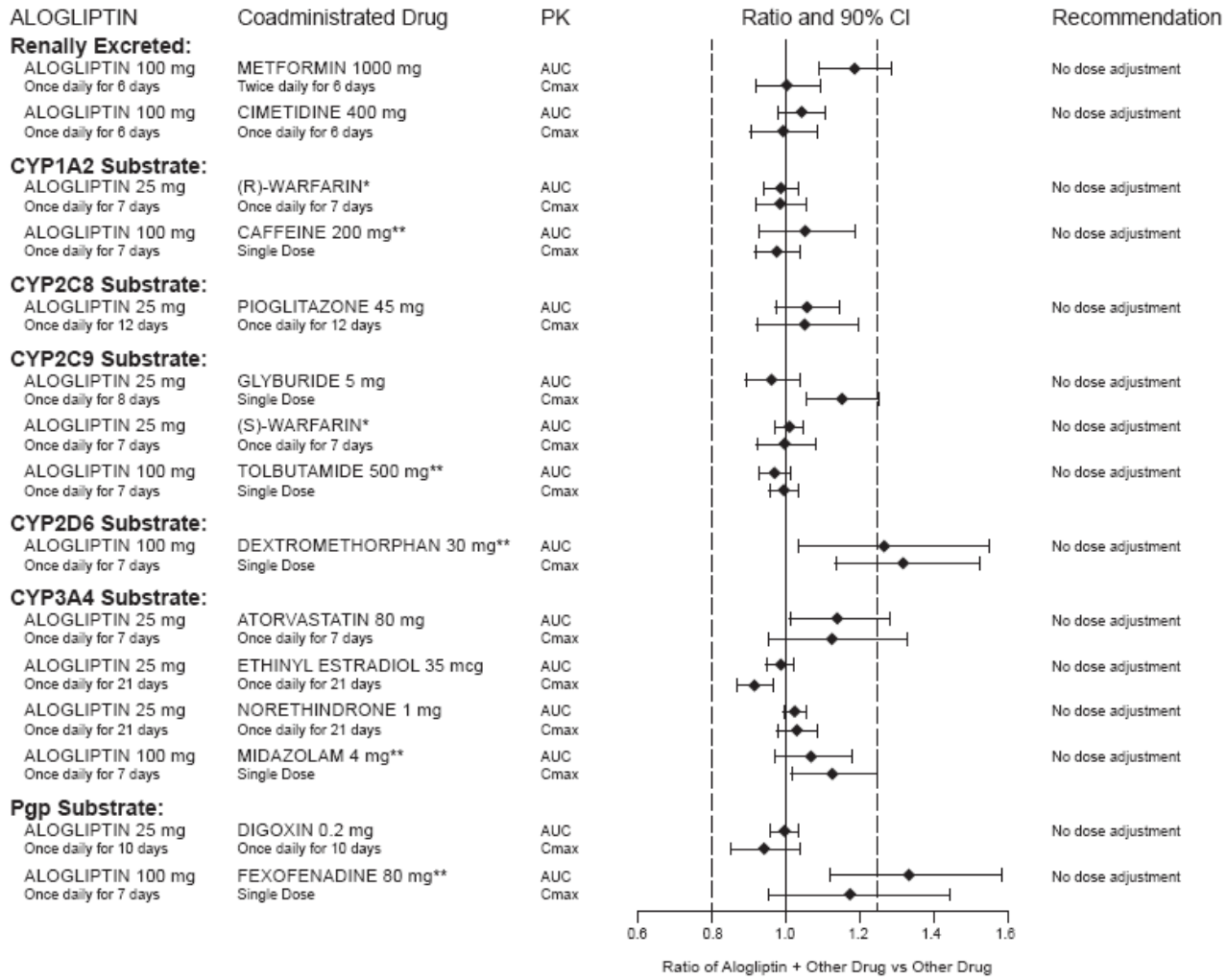
Metformin HCl
No pharmacokinetic studies of metformin have been conducted in subjects with hepatic impairment.

Drug Interaction Studies
Alogliptin and Metformin HCl
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 KAZANO have not been performed, although such studies have been conducted with the individual components of KAZANO (alogliptin and metformin).

Alogliptin
Clinical Studies
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**



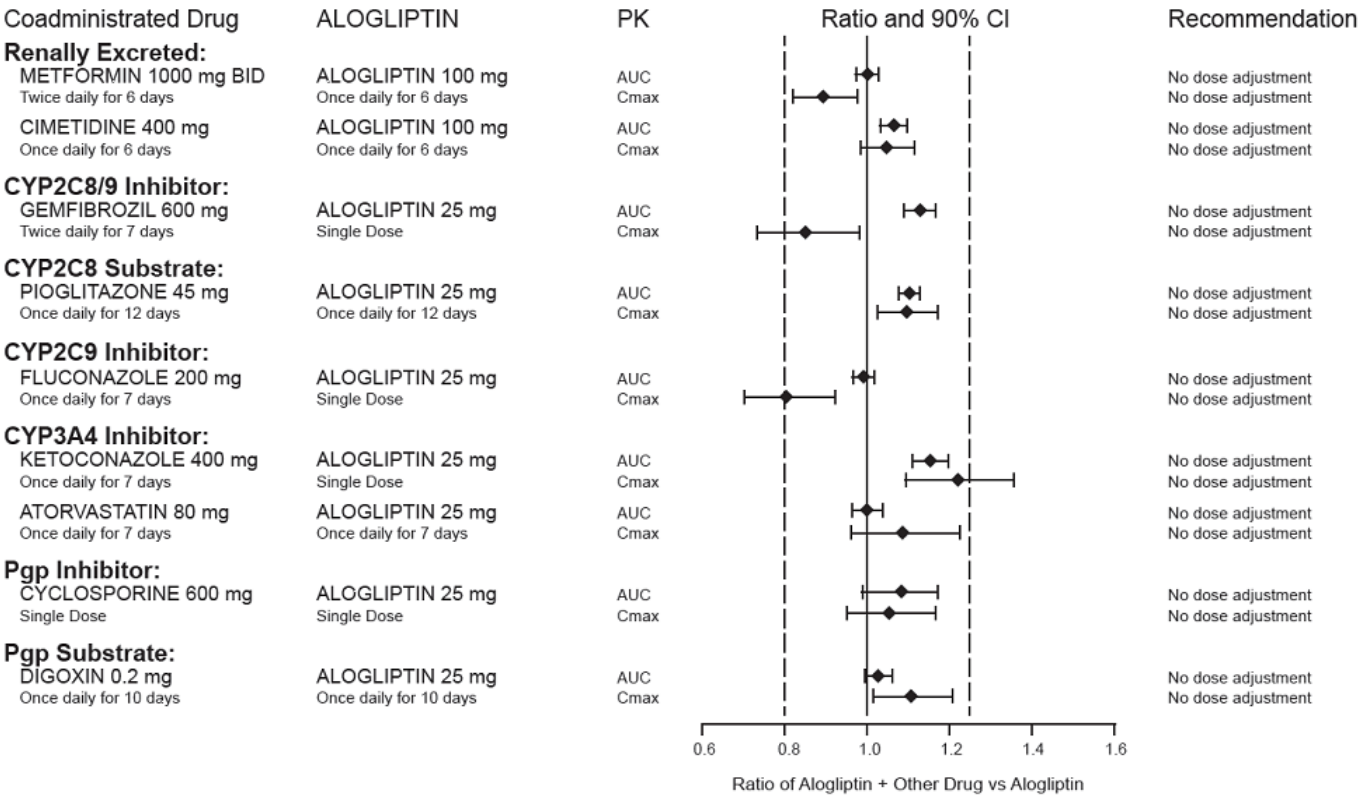
* Warfarin was given once daily at a stable dose in the range of 1 mg to 10 mg. Alogliptin had no significant effect on the prothrombin time (PT) or International Normalized Ratio (INR).

** 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*:Effect of Other Drugs on the Pharmacokinetic Exposure of Alogliptin*).*

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



Metformin HCl

Pharmacokinetic drug interaction studies have been performed on metformin *(*Table 4 *and Table 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), Drug Interactions (7)]*.				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis *[see Warnings and Precautions (5), 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 HCl 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 HCl

No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with KAZANO. 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 HCl

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

14.1 Overview of Clinical Trials in Adults with Type 2 Diabetes Mellitus

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

A total of 2,114 patients with type 2 diabetes mellitus were randomized in three double-blind, placebo- or active-controlled clinical safety and efficacy trials conducted to evaluate the effects of alogliptin co-administered with metformin HCl on glycemic control. Among those, 2,095 patients were exposed to the trial medication. The racial distribution of patients exposed to trial medication was 69% White, 16% Asian, 7% Black or African American, 2% American Indian or Alaska Native, 0% Native Hawaiian/Other Pacific Islander and 6% Multiracial or other racial groups. The ethnic distribution was 24% Hispanic or Latino. Patients had an overall mean age of approximately 54.4 years (range 22 to 80 years). In patients with type 2 diabetes mellitus, treatment with alogliptin co-administered with metformin HCl produced clinically meaningful and statistically significant improvements in A1C versus comparator. As is typical for trials of agents to treat type 2 diabetes mellitus, the mean reduction in hemoglobin A1c (A1C) with alogliptin co-administered with metformin HCl appears to be related to the degree of A1C elevation at baseline.

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

In a 26 week, double-blind, placebo-controlled trial, 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 3)* 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 co-administered with metformin HCl. Lipid effects were neutral.

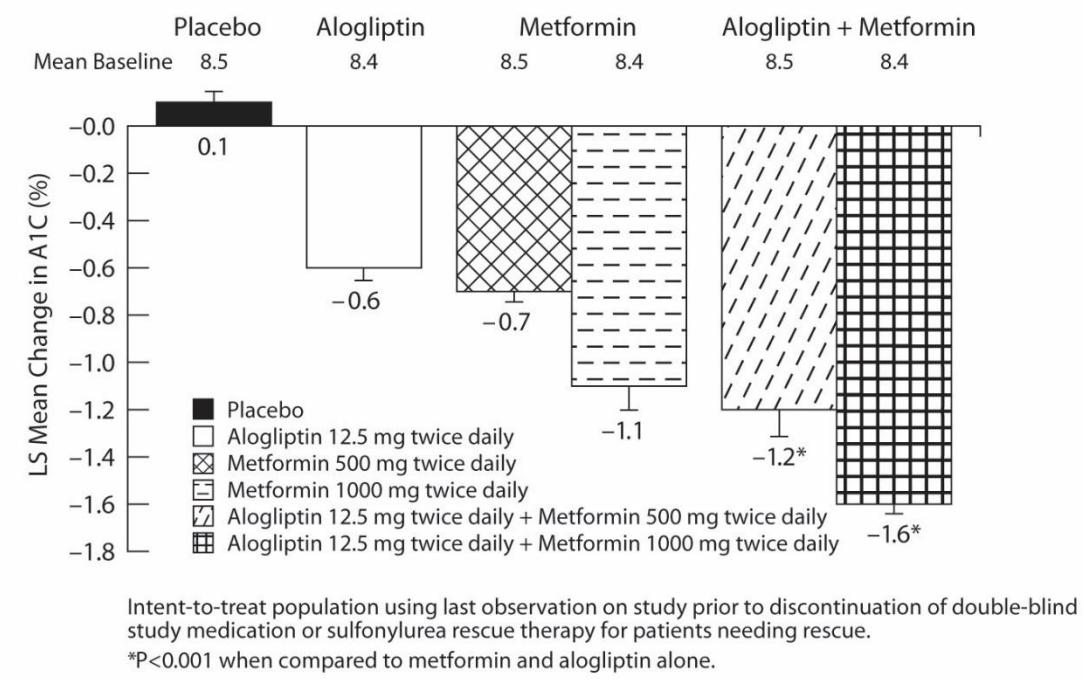
Table 6:**Glycemic Parameters at Week 26 for Alogliptin and Metformin HCl Alone and in Combination in Patients with Type 2 Diabetes Mellitus**

	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	-	-	-	-	-25 (-53, 3)	-43‡ (-70, -16)

mean† with 95% confidence interval)						

* Intent-to-treat population using last observation on trial prior to discontinuation of double-blind trial 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.

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

In a 26 week, double-blind, placebo-controlled trial, 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 Trial of Alogliptin as Add-on Therapy to Metformin in Adults with Type 2 Diabetes Mellitus***

	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 trial

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

‡ p<0.001 compared to placebo

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

In a 52 week, active-comparator trial, 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 Trial of Alogliptin as Add-On Combination Therapy to Metformin and Pioglitazone in Adults with Type 2 Diabetes Mellitus*

	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 trial

† 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

14.5 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 mellitus 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 mellitus 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%), White (73%), and were recruited from outside of the United States (86%). Asian and Black or African American 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 (83%) and renal impairment (27% with an eGFR ≤60 mL/min/1.73 m^2) were prevalent co-morbid conditions. Use of medications to treat diabetes mellitus (e.g., metformin 73%, sulfonylurea 54%, insulin 41%), and ASCVD (e.g., statin 94%, aspirin 93%, 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 mellitus 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 trial was designed to exclude a pre-specified risk margin of 1.3 for the hazard ratio of MACE. The median exposure to trial drug was 526 days and 95% of the patients were followed to trial completion or death.

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

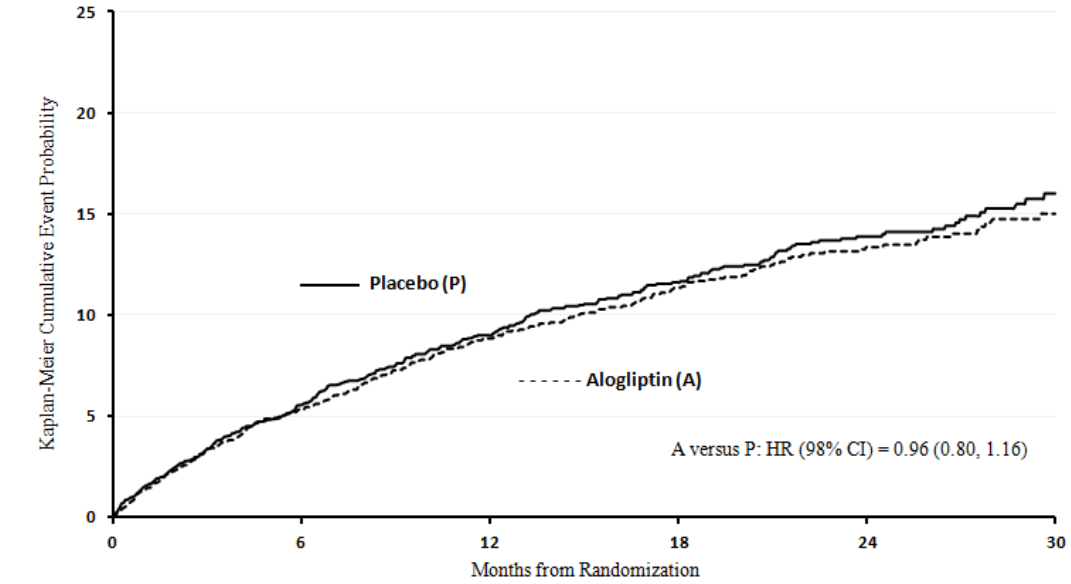
Table 9:**Patients with MACE in EXAMINE**

	Alogliptin		**Placebo**		**Hazard Ratio**
	Number of Patients (%)	**Rate per 100 PY***	**Number of Patients (%)**	**Rate per 100 PY***	**(98% CI)**
	N=2701		**N=2679**		
Composite of first event of CV death, nonfatal MI or nonfatal stroke (MACE)	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 trial. 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



At risk:						
A	2701	2316	1899	1394	821	296
P	2679	2299	1891	1375	805	286

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

KAZANO 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 64764-335-60	Bottles of 60 tablets
NDC 64764-335-80	Bottles of 180 tablets
NDC 64764-335-77	Bottles of 500 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 64764-337-60	Bottles of 60 tablets
NDC 64764-337-80	Bottles of 180 tablets
NDC 64764-337-77	Bottles of 500 tablets

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).

Lactic Acidosis
Explain the risks of lactic acidosis, its symptoms, and conditions that predispose to its development. Advise patients to discontinue KAZANO immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Counsel patients against excessive alcohol intake and inform patients about importance of regular testing of renal function while receiving KAZANO. Instruct patients to inform their doctor that they are taking KAZANO prior to any surgical or radiological procedure, as temporary discontinuation may be required *[see Warnings and Precautions (5.1)]*.

Pancreatitis
Inform patients that acute pancreatitis has been reported during use of alogliptin. Educate patients that persistent, severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to promptly discontinue KAZANO and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.2)]*.

Heart Failure
Inform patients of the signs and symptoms of heart failure. Before initiating KAZANO, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Instruct patients to contact their healthcare providers as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight, or swelling of the feet *[see Warnings and Precautions (5.3)]*.

Hypersensitivity Reactions
Inform patients that allergic reactions have been reported during use of alogliptin and metformin. Instruct patients 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 discontinue KAZANO and seek medical advice promptly *[see Warnings and Precautions (5.4)]*.

Hepatic Effects
Inform patients that postmarketing reports of liver injury, sometimes fatal, have been reported during use of alogliptin. Instruct patients that if signs or symptoms of liver injury occur, patients should be instructed to discontinue KAZANO and seek medical advice promptly *[see Warnings and Precautions (5.5)]*.

Vitamin B_{12} Deficiency
Inform patients about importance of regular hematological parameters while receiving metformin *[see Warnings and Precautions (5.6)]*.

Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues
Inform patients that hypoglycemia can occur, particularly when an insulin secretagogue or insulin is used in combination with KAZANO. Educate patients about the risks, symptoms and appropriate management of hypoglycemia *[see Warnings and Precautions (5.7)]*.

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

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

Dosage

Instruct patients to take KAZANO only as prescribed twice daily and that it should be taken with food. Instruct patients if a dose is missed, not to double their next dose. Instruct patients that the tablets must never be split.

Females of Reproductive Age

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)]*.

ALM143 R16

MEDICATION GUIDE
KAZANO® [Kah-ZAHN-oh]
(alogliptin and metformin HCl)
tablets, for oral use

Read this Medication Guide carefully before you start taking KAZANO 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 KAZANO, ask your doctor or pharmacist.

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

1. **Lactic Acidosis. Metformin, one of the medicines in KAZANO, 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 lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance of getting lactic acidosis with KAZANO 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
- have a genetically inherited disease affecting mitochondria (the energy-producing parts within cells) such as mitochondrial encephalomyopathy with lactic acidosis, and stroke-like episodes (MELAS) syndrome and maternally inherited diabetes and deafness (MIDD)

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. Your doctor may decide to stop KAZANO for a while if you have any of these things.

KAZANO can have other serious side effects. See “What are the possible side effects of KAZANO?”

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

Before you start taking KAZANO:
Tell your doctor if you have ever had:

- pancreatitis
- kidney problems
- liver problems
- high blood triglyceride levels
- stones in your gallbladder (gall stones)
- history of alcoholism

Stop taking KAZANO 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: Heart failure means your heart does not pump blood well enough.

Before you start taking KAZANO:

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
- unusual tiredness

These may be symptoms of heart failure.

What is KAZANO?

- KAZANO contains 2 prescription diabetes mellitus medicines, alogliptin (NESINA®) and metformin hydrochloride.
- KAZANO is a prescription medicine used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes mellitus.
- KAZANO is not for people with type 1 diabetes mellitus.

It is not known if KAZANO is safe and effective in children under the age of 18.

Who should not take KAZANO?
Do not take KAZANO 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, KAZANO may need to be stopped for a short time. Talk to your doctor about when you should stop KAZANO and when you should start KAZANO again
- are allergic to alogliptin (NESINA) or metformin or any of the ingredients in KAZANO 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 KAZANO

Symptoms of a serious allergic reaction to KAZANO 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 KAZANO 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 KAZANO?
Before you take KAZANO, 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, KAZANO may need to be stopped for a short time. Talk to your doctor about when you should stop KAZANO and when you should start KAZANO 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 KAZANO 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 if KAZANO passes into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking KAZANO
- have a genetically inherited disease affecting mitochondria (the energy-producing parts within cells) such as MELAS syndrome or MIDD

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.

KAZANO may affect the way other medicines work, and other medicines may affect how KAZANO works. Contact your doctor before you start or stop other types of medicines.

How should I take KAZANO?

- Take KAZANO exactly as your doctor tells you to take it.
- Take KAZANO 2 times each day.
- Take KAZANO with food to lower your chances of having an upset stomach.
- Do not break or cut KAZANO tablets before swallowing.
- Your doctor may need to change your dose of KAZANO 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 KAZANO at the same time.
- If you take too much KAZANO, call your doctor or your Poison Help Line right away at 1-800-222-1222.
- If your body is under stress, such as from fever, infection, accident or surgery, the dose of your diabetes mellitus 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 KAZANO and during treatment as needed. Your doctor may ask you to stop taking KAZANO based on the results of your blood tests due to how well your kidneys are working.
- Your doctor will check your diabetes mellitus with regular blood tests, including your blood sugar levels and your hemoglobin A1C.

What are the possible side effects of KAZANO?

KAZANO can cause serious side effects, including:

- See **"What is the most important information I should know about KAZANO?"**

Serious 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 KAZANO and contact your doctor right away or go to the nearest hospital emergency room.

- **Liver problems.** Call your doctor right away or go to the nearest hospital emergency room 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 Vitamin B_{12} levels (vitamin B_{12} deficiency).** Some people taking metformin one of the medicines in KAZANO had low levels of Vitamin B_{12}. Your doctor should do blood tests every year and check your Vitamin B_{12} levels every 2 to 3 years while you are taking KAZANO.
- **Low blood sugar (hypoglycemia).** If you take KAZANO 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 KAZANO. 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 KAZANO, 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 KAZANO, 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 KAZANO.

The most common side effects of KAZANO 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 KAZANO 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 effects that bother you or that does not go away.

These are not all the possible side effects of KAZANO. 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 KAZANO?

- Store KAZANO at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the container of KAZANO tightly closed.

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

General information about the safe and effective use of KAZANO

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

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

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

What are the ingredients in KAZANO?

Active ingredients: alogliptin and metformin hydrochloride

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

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