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 HCl) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: LACTIC ACIDOSIS
See full prescribing information for complete boxed warning

- **Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment and acute congestive heart failure. (5.1)**
- **Symptoms include malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. (5.1)**
- **If acidosis is suspected, discontinue KAZANO and hospitalize the patient immediately. (5.1)**

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

Indications and Usage (1.1)	4/2016
Warnings and Precautions	
Pancreatitis (5.2)	4/2016
Heart Failure (5.3)	4/2016
Hepatic Effects (5.5)	4/2016
Severe and Disabling Arthralgia (5.11)	8/2015

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

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

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

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

- Individualize the starting dose of KAZANO based on the patient's current regimen. (2.1)
- KAZANO should be taken twice daily with food. (2.1)
- May adjust the dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg alogliptin and 2000 mg metformin HCl. (2.1)

----------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----------

- Renal impairment. (4, 5.5)
- Metabolic acidosis, including diabetic ketoacidosis. (4, 5.1)
- History of a serious hypersensitivity reaction to alogliptin or metformin, components of KAZANO, such as anaphylaxis, angioedema or severe cutaneous adverse reactions. (4)

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

- Lactic acidosis: Warn against excessive alcohol intake. KAZANO is not recommended in hepatic impairment and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter. (5.1)
- Acute 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. In such cases, promptly discontinue KAZANO, assess for other potential causes, institute appropriate monitoring and treatment and initiate alternative treatment for diabetes. (5.4)
- Hepatic effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt 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)
- Temporarily discontinue in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids. (5.6)
- Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually. (5.9)
- Hypoglycemia: When used with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia. (5.10)
- 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. (5.11)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KAZANO or any other antidiabetic drug. (5.12)

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

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

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

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

Cationic drugs eliminated by renal tubular secretion: Use with caution. (7.2)

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

- Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. (8.1)
- Pediatrics: Safety and effectiveness of KAZANO in patients below the age of 18 have not been established. (8.4)
- Geriatric Use: Caution should be used when prescribing KAZANO to elderly patients because reduced renal functions are associated with increasing age. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2016

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

- **Lactic acidosis is a rare but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment and acute congestive heart failure *[see Warnings and Precautions (5.1)].***
- **The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate *[see Warnings and Precautions (5.1)].***
- **If acidosis is suspected, KAZANO (alogliptin and metformin HCl) should be discontinued and the patient hospitalized immediately *[see Warnings and Precautions (5.1)].***

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

KAZANO is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both alogliptin and metformin is appropriate *[see Clinical Studies (14)]*.

Important Limitations of Use

KAZANO is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommendations for All Patients

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

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:

- Renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction and septicemia *[see Warnings and Precautions (5.6)].*
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to alogliptin or metformin, components of KAZANO, such as anaphylaxis, angioedema or severe cutaneous adverse reactions.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

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

The reported incidence of lactic acidosis in patients receiving metformin HCl is very low (approximately 0.03 cases per 1000 patient-years, with approximately 0.015 fatal cases per 1000 patient-years). In more than 20,000 patient-years’ exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, particularly when accompanied by hypoperfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient’s age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in any patients unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking metformin, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical

procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent metabolic acidosis (in controlled trials, 32% and 67% for adjunctive treatment in adult and pediatric patients, respectively, and 15% to 25% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 20 mEq/L; 3% and 11% for adjunctive treatment in adult and pediatric patients, respectively, and 1% to 7% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 17 mEq/L) and may exacerbate the risk of metformin-induced lactic acidosis *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

The onset of lactic acidosis often is subtle and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis.

Patients should be educated to promptly report these symptoms should they occur. If present, KAZANO should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels and blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, GI symptoms, which are common during initiation of therapy, are unlikely to recur. Later occurrence of GI symptoms could be due to lactic acidosis or other serious disease.

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

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

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery *[see Contraindications (4)].*

5.2 Pancreatitis

Acute pancreatitis has been reported in the postmarketing setting and in randomized clinical trials. In glycemic control trials in patients with type 2 diabetes, acute pancreatitis was reported in 6 (0.2%) patients treated with alogliptin 25 mg and 2 (<0.1%) patients treated with active comparators or placebo. In the EXAMINE trial (a cardiovascular outcomes trial of patients with type 2 diabetes and high cardiovascular (CV) risk), acute pancreatitis was reported in 10 (0.4%) of patients treated with alogliptin and in 7 (0.3%) of 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 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. 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 *[see Adverse Reactions (6.3)]*. Use caution in patients with a history of angioedema with another dipeptidyl peptidase-4 (DPP-4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with 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 (6.3)].*

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

Because impaired hepatic function has been associated with some cases of lactic acidosis with use of metformin, KAZANO should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

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 Monitoring of Renal Function

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment. Therefore, KAZANO is contraindicated in patients with renal impairment.

Before initiation of KAZANO therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and KAZANO discontinued if evidence of renal impairment is present. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis.

Use of Concomitant Medications that May Affect Renal Function or Metformin Disposition

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion *[see Drug Interactions (7.2)]*, should be used with caution.

Radiological Studies and Surgical Procedures

Radiological studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography and computed tomography) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, KAZANO should be temporarily discontinued at the time of or prior to the procedure and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

KAZANO therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient’s oral intake has resumed and renal function has been evaluated as normal.

5.7 Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on KAZANO therapy, the drug should be promptly discontinued.

5.8 Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake while receiving KAZANO.

5.9 Vitamin B_{12} Levels

In controlled, 29-week clinical trials of immediate-release metformin, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on KAZANO, and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at two- to three-year intervals may be useful.

5.10 Use with Medications Known to Cause Hypoglycemia

Alogliptin

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

Metformin Hydrochloride

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

5.11 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.

5.12 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KAZANO or any other antidiabetic drug.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

1. Pancreatitis *[see Warnings and Precautions (5.2)]*
2. Heart Failure *[see Warnings and Precautions (5.3)]*
3. Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*
4. Hepatic Effects *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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

Alogliptin and Metformin Hydrochloride

Over 2700 patients with type 2 diabetes have received alogliptin coadministered with metformin in four large, randomized, double-blind controlled clinical trials. The mean exposure to KAZANO was 58 weeks, with more than 1400 subjects treated for more than one year. These included two 26-week placebo-controlled studies, one 52-week active control study and an interim analysis of a 104-week active-controlled study. In the KAZANO arm, the mean duration of diabetes 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 KAZANO compared to 75% treated with placebo. Overall discontinuation of therapy due to adverse reactions was 6.2% with KAZANO compared to 1.9% in placebo, 6.4% in metformin and 5.0% in alogliptin.

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

Table 1. Adverse Reactions Reported in ≥4% of Patients Treated with KAZANO and More Frequently Than in Patients Receiving Either Alogliptin, Metformin or Placebo				
	Number of Patients (%)			
	KAZANO*	Alogliptin†	Metformin‡	Placebo
	N=2794	N=222	N=1592	N=106
Upper respiratory tract infection	224 (8.0)	6 (2.7)	105 (6.6)	3 (2.8)
Nasopharyngitis	191 (6.8)	7 (3.2)	93 (5.8)	2 (1.9)
Diarrhea	155 (5.5)	4 (1.8)	105 (6.6)	3 (2.8)
Hypertension	154 (5.5)	5 (2.3)	96 (6.0)	6 (5.7)
Headache	149 (5.3)	11 (5.0)	74 (4.6)	3 (2.8)
Back pain	119 (4.3)	1 (0.5)	72 (4.5)	1 (0.9)
Urinary tract infection	116 (4.2)	4 (1.8)	59 (3.7)	2 (1.9)

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

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

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

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

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

Alogliptin
A total of 14,778 patients with type 2 diabetes participated in 14 randomized, double-blind, controlled clinical trials of whom 9052 subjects were treated with alogliptin, 3469 subjects were treated with placebo and 2257 were treated with an active comparator. The mean duration of diabetes was seven

years, the mean body mass index (BMI) was 31 kg/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 3348 subjects treated for more than one year.

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

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

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

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

Hypoglycemia

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

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

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

Metformin Hydrochloride

Table 3. Most Common Adverse Reactions (≥5%) in a Placebo-Controlled Clinical Study of Metformin Monotherapy*		
Adverse Reaction	**Metformin Monotherapy (n=141)**	**Placebo (n=145)**
	% of Patients	
Diarrhea	53.2	11.7
Nausea/vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal discomfort	6.4	4.8
Headache	5.7	4.8

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

6.2 Laboratory Abnormalities

Alogliptin and Metformin Hydrochloride

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

Metformin Hydrochloride

Metformin may lower serum vitamin B_{12} concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on KAZANO, and any apparent abnormalities should be appropriately investigated and managed *[see Warnings and Precautions (5.9)].*

6.3 Postmarketing Experience

Alogliptin

The following adverse reactions have been identified during the postmarketing use of alogliptin. 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.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria and severe cutaneous adverse reactions, including Stevens-Johnson syndrome, hepatic enzyme elevations, fulminant hepatic failure, severe and disabling arthralgia, acute pancreatitis, diarrhea, constipation, nausea, and ileus *[see Warnings and Precautions (5.2, 5.4, 5.5, 5.11)*.

7 DRUG INTERACTIONS

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

Metformin Hydrochloride

7.1 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce nonanion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with metformin, as the risk of lactic acidosis may increase.

7.2 Cationic Drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of KAZANO and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

7.3 The Use of Metformin with Other Drugs

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs and isoniazid. When such drugs are administered to a patient receiving 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B
Alogliptin and Metformin Hydrochloride
There are no adequate and well-controlled studies in pregnant women with KAZANO or its individual components. Based on animal data, KAZANO is not predicted to increase the risk of developmental abnormalities. Because animal reproduction studies are not always predictive of human risk and exposure, KAZANO, like other antidiabetic medications, should be used during pregnancy only if clearly needed.

No treatment-related fetal abnormalities occurred following concomitant administration of 100 mg/kg alogliptin with 150 mg/kg metformin to pregnant rats, or approximately 28 and two times the clinical dose of alogliptin (25 mg) and metformin (2000 mg), respectively (based on AUC).

Alogliptin
Alogliptin administered to pregnant rabbits and rats during the period of organogenesis was not teratogenic at doses of up to 200 mg/kg and 500 mg/kg, or 149 times and 180 times, respectively, the clinical dose based on plasma drug exposure (AUC).

Doses of alogliptin up to 250 mg/kg (approximately 95 times clinical exposure based on AUC) given to pregnant rats from gestation Day 6 to lactation Day 20 did not harm the developing embryo or adversely affect growth and development of offspring.

Placental transfer of alogliptin into the fetus was observed following oral dosing to pregnant rats.

Metformin Hydrochloride
Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg, which represents an exposure of about two and six times the MRHD dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Metformin HCl should not be used during pregnancy unless clearly needed.

8.3 Nursing Mothers
No studies have been conducted with the combined components of KAZANO. In studies performed with the individual components, both alogliptin and metformin are secreted in the milk of lactating rats. It is not known whether alogliptin and/or metformin are secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when KAZANO is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness of KAZANO in pediatric patients have not been established.

8.5 Geriatric Use
Alogliptin and Metformin Hydrochloride
Elderly patients are more likely to have decreased renal function. Because metformin is contraindicated in patients with renal impairment, carefully monitor renal function in the elderly and use KAZANO with caution as age increases *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*.

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

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

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

Metformin should only be used in patients with normal renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age due to the potential for decreased renal function in this population *[see Contraindications (4), Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)].*

10 OVERDOSAGE

Alogliptin

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

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

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

Metformin Hydrochloride

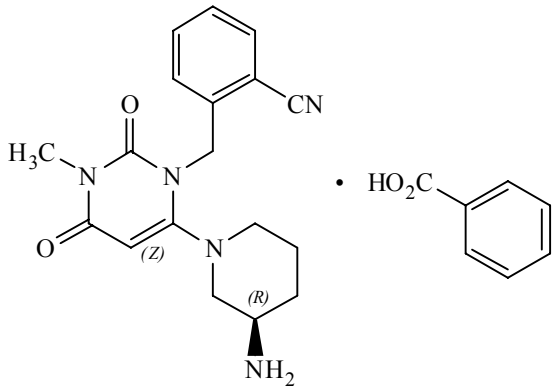
Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases *[see Warnings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

11 DESCRIPTION

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

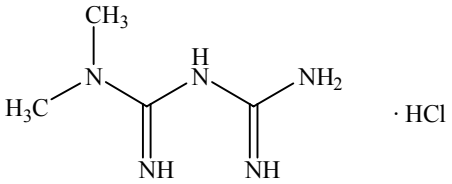
Alogliptin

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



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

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



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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Alogliptin

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Alogliptin is a DPP-4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus. Alogliptin selectively binds to and inhibits DPP-4 but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Metformin Hydrochloride

Metformin is a biguanide that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in patients with type 2 diabetes or in healthy subjects except in special circumstances *[see Warnings and Precautions (5.10)]* and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.

12.2 Pharmacodynamics

Alogliptin

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

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

12.3 Pharmacokinetics

Absorption and Bioavailability

Alogliptin and Metformin Hydrochloride

In bioequivalence studies of KAZANO, the area under the plasma concentration curve (AUC) and maximum concentration (C_{max}) of both the alogliptin and the metformin component following a single dose of the combination tablet were bioequivalent to the alogliptin 12.5 mg concomitantly administered with metformin HCl 500 or 1000 mg tablets under fasted conditions in healthy subjects. Administration of 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
The absolute bioavailability of alogliptin is approximately 100%. Administration of alogliptin with a high-fat meal results in no significant change in total and peak exposure to alogliptin. Alogliptin may therefore be administered with or without food.

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

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

Alogliptin is 20% bound to plasma proteins.

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

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

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

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

Metformin Hydrochloride

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

Excretion and Elimination

Alogliptin

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

Metformin Hydrochloride

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

Special Populations

Renal Impairment

Alogliptin and Metformin Hydrochloride

Use of KAZANO in patients with renal impairment increases the risk for lactic acidosis. Because KAZANO contains metformin, KAZANO is contraindicated in patients with renal impairment *[see Contraindications (4) and Warnings and Precautions (5.6)].*

Hepatic Impairment

KAZANO is not recommended in patients with hepatic impairment. KAZANO contains metformin and use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis *[see Warnings and Precautions (5.5)].*

Alogliptin

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

Metformin Hydrochloride

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

Gender

Alogliptin

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

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

Geriatric
KAZANO contains metformin, which is contraindicated in patients with renal impairment *[see Warnings and Precautions (5.6)]*. Due to declining renal function in the elderly, measurement of creatinine clearance should be obtained prior to initiation of therapy. Do not use KAZANO if renal function is not within normal range.

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

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

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

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

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

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

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

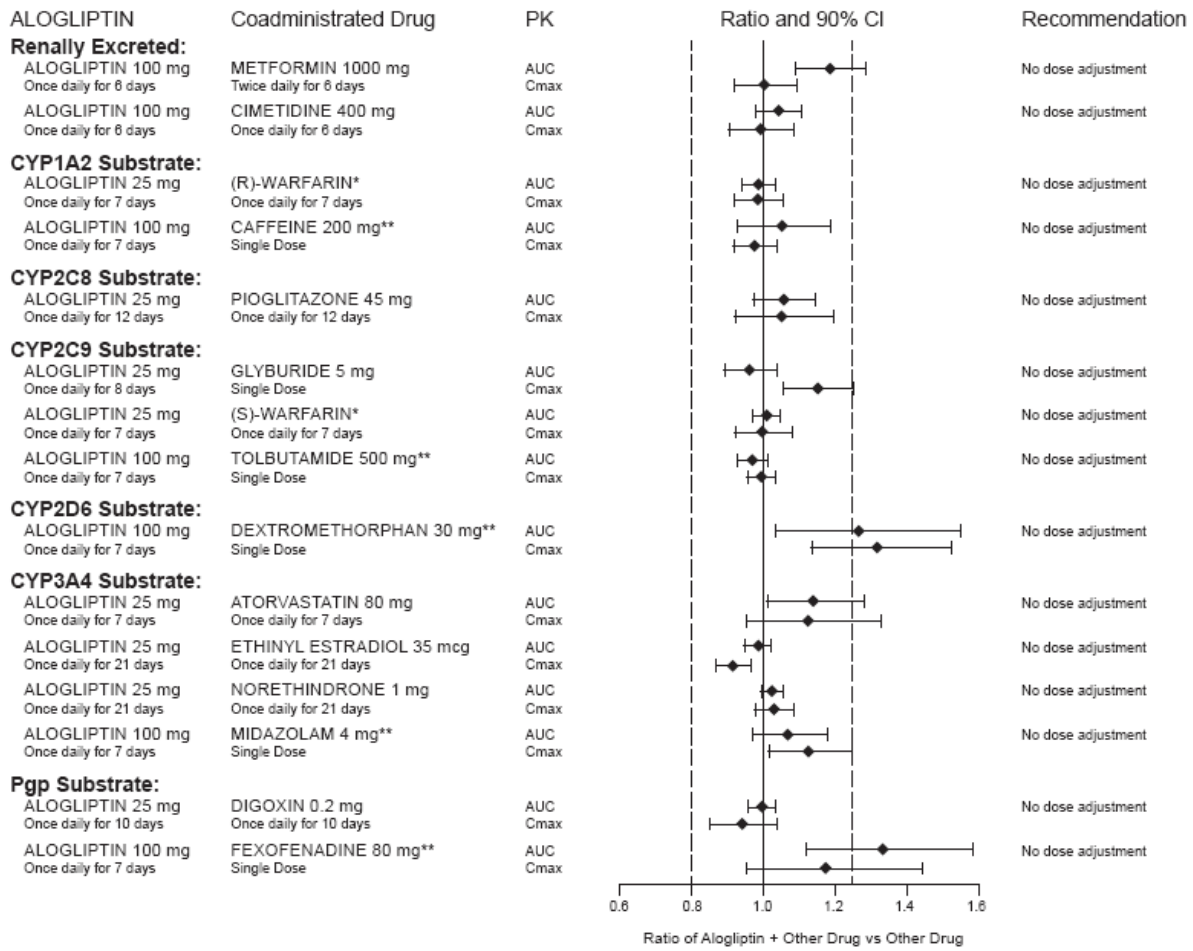
Alogliptin
***In Vitro* Assessment of Drug Interactions**
In vitro studies indicate that alogliptin is neither an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4, nor an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP2D6 at clinically relevant concentrations.

In Vivo Assessment of Drug Interactions

Effects of Alogliptin on the Pharmacokinetics of Other Drugs

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

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

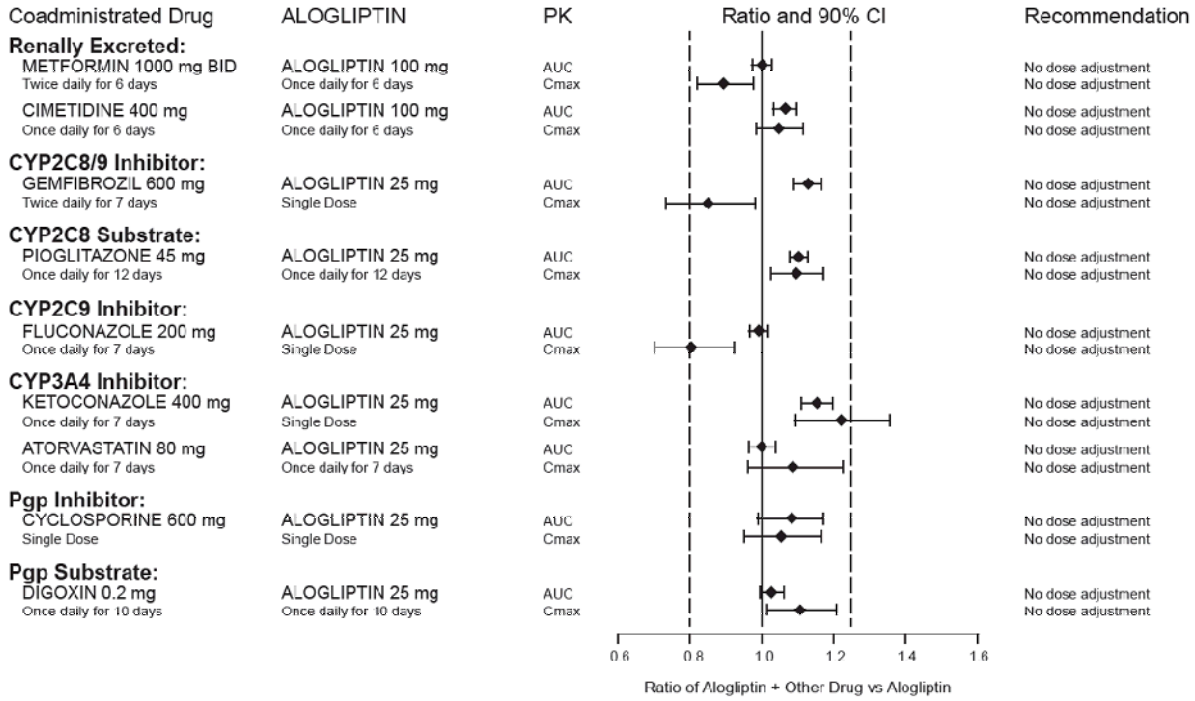


*Warfarin was given once daily at a stable dose in the range of 1 mg to 10 mg. Alogliptin had no significant effect on the prothrombin time (PT) or International Normalized Ratio (INR).
**Caffeine (1A2 substrate), tolbutamide (2C9 substrate), dextromethorphan (2D6 substrate), midazolam (3A4 substrate)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

Effects of Other Drugs on the Pharmacokinetics of Alogliptin

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

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



Metformin Hydrochloride

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

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

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.00	
			AUC[†]	C_{max}
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg[‡]	0.98[§]	0.99[§]
Furosemide	40 mg	850 mg	1.09[§]	1.22[§]
Nifedipine	10 mg	850 mg	1.16	1.21
Propranolol	40 mg	850 mg	0.90	0.94
Ibuprofen	400 mg	850 mg	1.05[§]	1.07[§]
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution *[see Warnings and Precautions (5) and Drug Interactions (7)]*				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution *[see Warnings and Precautions (5) and Drug Interactions (7)]*				
Topiramate	100 mg[¶]	500 mg[¶]	1.25[¶]	1.17

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

Table 5. Effect of Metformin on Coadministered Drug Systemic Exposure				
Coadministered Drug	**Dose of Coadministered Drug***	**Dose of Metformin HCl***	**Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.00**	
			AUC†	**C_{max}**
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg‡	0.78§	0.63§
Furosemide	40 mg	850 mg	0.87§	0.69§
Nifedipine	10 mg	850 mg	1.10‡	1.08
Propranolol	40 mg	850 mg	1.01‡	0.94
Ibuprofen	400 mg	850 mg	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	0.95‡	1.01

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Alogliptin and Metformin Hydrochloride

No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with 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 Hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg and 1500 mg/kg, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg.

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

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

14 CLINICAL STUDIES

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

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

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

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

In a 26-week, double-blind, placebo-controlled study, a total of 784 patients inadequately controlled on diet and exercise alone (mean baseline A1C = 8.4%) were randomized to one of seven treatment groups: placebo; metformin HCl 500 mg or metformin HCl 1000 mg twice daily, alogliptin 12.5 mg twice daily, or alogliptin 25 mg daily; alogliptin 12.5 mg in combination with metformin HCl 500 mg or metformin HCl 1000 mg twice daily. Both coadministration treatment arms (alogliptin 12.5 mg + metformin HCl 500 mg and alogliptin 12.5 mg + metformin HCl 1000 mg) resulted in significant improvements in A1C *(Figure 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.

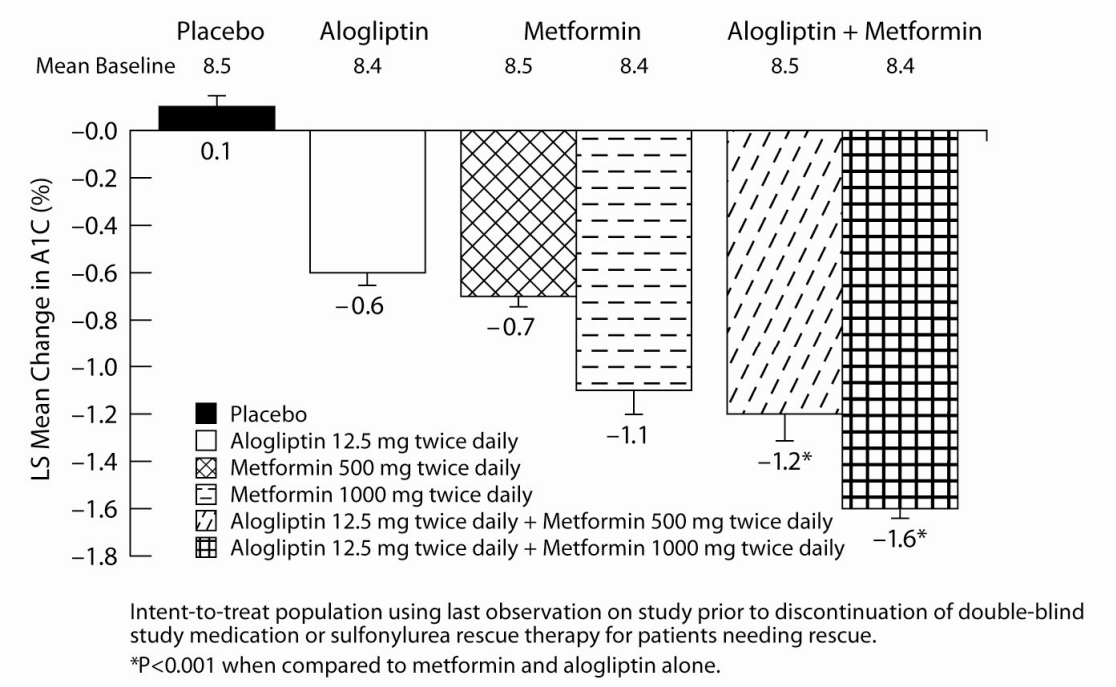
Improvements in A1C were not affected by gender, age, race or baseline BMI. The mean decrease in body weight was similar between metformin alone and alogliptin when coadministered with metformin. Lipid effects were neutral.

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

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

*Intent-to-treat population using last observation on study prior to discontinuation of double-blind study medication or sulfonylurea rescue therapy for patients needing rescue
[†]Least squares means adjusted for treatment, geographic region and baseline value
[‡]$p<0.05$ when compared to metformin and alogliptin alone
[§]Compared using logistic regression
[¶]Intent-to-treat population using data available at Week 26

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



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

*P<0.001 when compared to metformin and alogliptin alone.

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

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

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

Table 7. Glycemic Parameters at Week 26 in a Placebo-Controlled Study of Alogliptin as Add-on Therapy to Metformin*		
	Alogliptin 25 mg + Metformin	**Placebo + Metformin**
A1C (%)	**N=203**	**N=103**
Baseline (mean)	7.9	8.0
Change from baseline (adjusted mean†)	-0.6	-0.1
Difference from placebo (adjusted mean† with 95% confidence interval)	-0.5‡ (-0.7, -0.3)	
% of patients (n/N) achieving A1C ≤7%‡	44% (92/207)‡	18% (19/104)
FPG (mg/dL)	**N=204**	**N=104**
Baseline (mean)	172	180
Change from baseline (adjusted mean†)	-17	0
Difference from placebo (adjusted mean† with 95% confidence interval)	-17‡ (-26, -9)	

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

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

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

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

The mean increase in body weight was similar in both treatment arms. Lipid effects were neutral.

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

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

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

Cardiovascular Safety Trial

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

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

The mean age of the population was 61 years. Most patients were male (68%), Caucasian (73%), and were recruited from outside of the United States (86%). Asian and Black patients contributed 20% and 4% of the total population, respectively. At the time of randomization patients had a diagnosis of type 2 diabetes mellitus for approximately 9 years, 87% had a prior myocardial infarction and 14% were current smokers. Hypertension (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 (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 and ASCVD could be adjusted to ensure care for these conditions adhered to standard of care recommendations set by local practice guidelines.

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

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

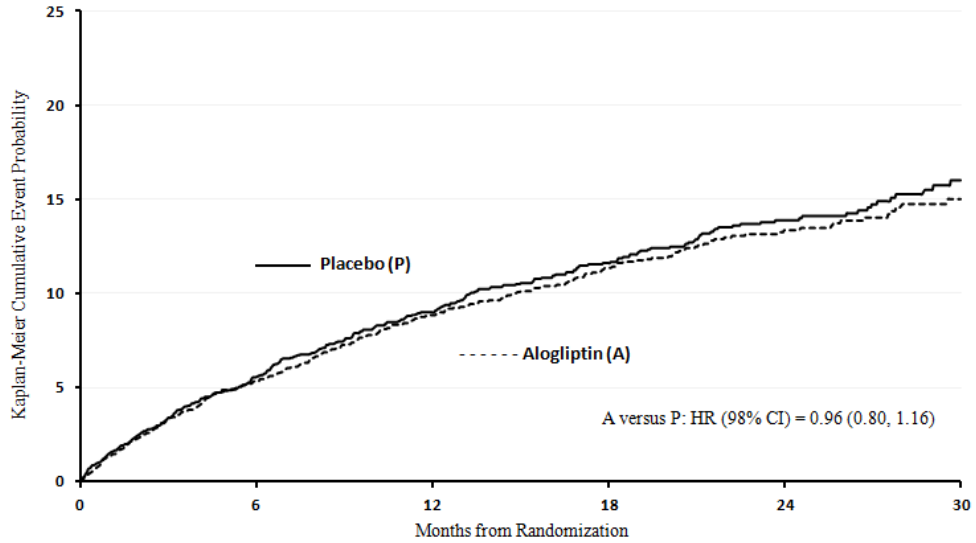
Table 9. Patients with MACE in EXAMINE

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

*Patient Years (PY)

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

Figure 4. Observed Cumulative Rate of MACE in EXAMINE



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

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

17 PATIENT COUNSELING INFORMATION

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

- Inform patients of the potential risks and benefits of KAZANO.

- The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in *Warnings and Precautions (5.1)*, should be explained to patients. Patients should be advised to discontinue KAZANO immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of KAZANO, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.
- Patients should be informed that acute pancreatitis has been reported during use of alogliptin. Patients should be informed that persistent, severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue KAZANO and contact their physician if persistent severe abdominal pain occurs.
- Patients should be informed 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. Patients should be instructed 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.
- Patients should be informed that allergic reactions have been reported during use of alogliptin and metformin. If symptoms of allergic reactions (including skin rash, hives and swelling of the face, lips, tongue and throat that may cause difficulty in breathing or swallowing) occur, patients should be instructed to discontinue KAZANO and seek medical advice promptly.
- Patients should be informed that postmarketing reports of liver injury, sometimes fatal, have been reported during use of alogliptin. If signs or symptoms of liver injury occur, patients should be instructed to discontinue KAZANO and seek medical advice promptly.
- Patients should be informed about the importance of regular testing of renal function and hematological parameters when receiving treatment with KAZANO.
- Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving KAZANO.
- Inform patients that hypoglycemia can occur, particularly when an insulin secretagogue or insulin is used in combination with KAZANO. Explain the risks, symptoms and appropriate management of hypoglycemia.
- Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs.
- Instruct patients to take KAZANO only as prescribed twice daily. KAZANO should be taken with food. If a dose is missed, advise patients not to double their next dose.
- Patients should be informed that the tablets must never be split.

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

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MEDICATION GUIDE
KAZANO (Kah-ZAHN-oh)
(alogliptin and metformin HCl)
tablets

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.

Stop taking KAZANO and call your doctor right away if you get any of the following symptoms of lactic acidosis:

- feel very weak or tired
- have trouble breathing
- have unexplained stomach or intestinal problems with nausea and vomiting, or diarrhea
- feel dizzy or lightheaded
- have unusual (not normal) muscle pain
- have unusual sleepiness or sleep longer than usual
- feel cold, especially in your arms and legs
- have a slow or irregular heartbeat

You have a higher chance for getting lactic acidosis with KAZANO if you:

- have kidney problems. People whose kidneys are not working properly should not take KAZANO
- have liver problems
- have congestive heart failure that requires treatment with medicines
- drink a lot of alcohol (very often or short-term “binge” drinking)
- get 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 certain x-ray tests with injectable dyes or contrast agents
- have surgery
- have a heart attack, severe infection or stroke

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

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:**

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

These may be symptoms of heart failure.

What is KAZANO?

- KAZANO contains 2 prescription diabetes 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.
- KAZANO is not for people with type 1 diabetes.

- KAZANO is not for people with diabetic ketoacidosis (increased ketones in blood or urine).

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 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 will 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
- raised, red areas on your skin (hives)
- difficulty with swallowing or breathing
- 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 kidney or liver problems
- have heart problems, including congestive heart failure
- are older than 80 years, you should not take KAZANO unless your kidneys have been checked and they are normal
- drink alcohol very often or drink a lot of alcohol in short-term “binge” drinking
- 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 whether KAZANO passes into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking KAZANO

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 go to the nearest hospital emergency room right away.
- If your body is under stress, such as from fever, infection, accident or surgery, the dose of your diabetes medicines may need to be changed. Call your doctor right away.
- Stay on your diet and exercise programs and check your blood sugar as your doctor tells you to.
- Your doctor may do certain blood tests before you start 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 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?"**
- **Allergic (hypersensitivity) reactions,** such as:
  - swelling of your face, lips, throat and other areas on your skin
  - raised, red areas on your skin (hives)
  - difficulty swallowing or breathing
  - skin rash, itching, flaking or peeling

  If you have these symptoms, stop taking KAZANO and contact your doctor right away.
- **Liver problems.** Call your doctor right away if you have unexplained symptoms, such as:
  - nausea or vomiting
  - stomach pain
  - unusual or unexplained tiredness
  - loss of appetite
  - dark urine
  - yellowing of your skin or the whites of your eyes
- **Low blood sugar (hypoglycemia).** If you take 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.

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

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