

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.

- Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/mL. (5.1)
- Risk factors include renal impairment, concomitant use of certain drugs, age ≥ 65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)
- If lactic acidosis is suspected, discontinue KAZANO and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

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 based on the patient's current regimen. (2.1)
- Give twice daily with food. (2.1)
- Adjust the dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg alogliptin and 2000 mg metformin HCl. (2.1)
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) (2.2)
 - Do not use in patients with eGFR below 60 mL/min/1.73 m².
- 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 m². (4)
- Metabolic acidosis, including diabetic ketoacidosis. (4)
- 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: See boxed warning. (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)
- Vitamin B₁₂ deficiency: Metformin may lower vitamin B₁₂ levels. Monitor hematologic parameters annually. (5.6)
- Hypoglycemia: When used with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia. (5.7)
- Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.8)
- Bullous pemphigoid: There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue KAZANO. (5.9)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KAZANO or any other antidiabetic drug. (5.10)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- Carbionic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.1)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine), may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7.2)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.3)

USE IN SPECIFIC POPULATIONS

- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy. (8.3)
- Pediatrics: Safety and effectiveness of KAZANO in patients below the age of 18 have not been established. (8.4)
- Geriatric Use: Assess renal function more frequently. (8.5)
- Hepatic Impairment: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 2/2017

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

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

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information [see *Dosage and Administration (2.2)*, *Contraindications (4)*, *Warnings and Precautions (5.1)*, *Drug Interactions (7)*, and *Use in Specific Populations (8.6, 8.7)*].

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

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

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

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 m² [see *Contraindications (4) and Warnings and Precautions (5.1)*].

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

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 m²; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart 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 m²) [see *Warnings and Precautions (5.1)*].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to alogliptin or metformin, components of KAZANO, such as anaphylaxis, angioedema or severe cutaneous adverse reactions.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Lactic Acidosis

There have been postmarketing cases of metformin-associated lactic-acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate:pyruvate ratio; metformin plasma levels generally greater than 5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be

instituted promptly in a hospital setting, along with immediate discontinuation of 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 hydrochloride is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue 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 m² [see *Contraindications (4)*].
- KAZANO is not recommended in patients with an eGFR between 30 and 60 mL/min/1.73 m² because these patients require a lower dosage of alogliptin than what is available in the fixed combination 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 m²; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart KAZANO if renal function is stable.

Surgery and Other Procedures

Withholding of food and fluids during surgical or other procedures may increase the risk for volume

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