

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KOMBIGLYZE XR safely and effectively. See full prescribing information for KOMBIGLYZE XR.

KOMBIGLYZE XR (saxagliptin and metformin hydrochloride extended-release) tablets, for oral use
Initial U.S. Approval: 2010

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- 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 KOMBIGLYZE XR and hospitalize the patient immediately. (5.1)

INDICATIONS AND USAGE

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

Limitations of Use:

- Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1.1)
- Has not been studied in patients with a history of pancreatitis. (1.1, 5.2)

DOSAGE AND ADMINISTRATION

- Administer once daily with the evening meal. (2.1)
- Individualize the starting dose based on the patient's current regimen then adjust the dosage based on effectiveness and tolerability. (2.1)
- Do not exceed a daily dosage of 5 mg saxagliptin/2000 mg metformin HCl extended-release. (2.1)
- Swallow whole. Never crush, cut, or chew. (2.1)
- Limit the saxagliptin dosage to 2.5 mg daily for patients also taking strong cytochrome P450 3A4/5 inhibitors (e.g., ketoconazole). (2.2, 7.1)

DOSAGE FORMS AND STRENGTHS

Tablets:

- 5 mg saxagliptin/500 mg metformin HCl extended-release (3)
- 5 mg saxagliptin/1000 mg metformin HCl extended-release (3)
- 2.5 mg saxagliptin/1000 mg metformin HCl extended-release (3)

CONTRAINDICATIONS

- Renal impairment. (4)
- Hypersensitivity to metformin hydrochloride. (4)
- Metabolic acidosis, including diabetic ketoacidosis. (4, 5.1)
- History of a serious hypersensitivity reaction (e.g., anaphylaxis, angioedema, exfoliative skin conditions) to KOMBIGLYZE XR or saxagliptin. (4)

WARNINGS AND PRECAUTIONS

- Lactic Acidosis: Warn patients against excessive alcohol intake. KOMBIGLYZE XR is not recommended in hepatic impairment and contraindicated in renal impairment. Ensure normal renal function

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before initiating and at least annually thereafter. Temporarily discontinue KOMBIGLYZE XR in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids. (4, 5.1, 5.3, 5.4, 5.7, 5.10, 5.11)

- Acute Pancreatitis (postmarketing reports): If pancreatitis is suspected, promptly discontinue KOMBIGLYZE XR. (5.2, 6.2)
- Vitamin B¹² Deficiency: Metformin may lower vitamin B¹² levels. Measure hematological parameters annually. (5.5, 6.1)
- Hypoglycemia: In the saxagliptin add-on to sulfonylurea, add-on to insulin, and add-on to metformin plus sulfonylurea trials, confirmed hypoglycemia was reported more commonly in patients treated with saxagliptin compared to placebo. When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. (5.9, 6.1)
- Hypersensitivity-Related Events (e.g., urticaria, facial edema): More common in patients treated with saxagliptin than in patients treated with placebo; and postmarketing reports of serious hypersensitivity reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions in patients treated with saxagliptin. Promptly discontinue KOMBIGLYZE XR, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.13, 6.1, 6.2)
- Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.14)
- Macrovascular Outcomes: No conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR or any other antidiabetic drug. (5.15)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Coadministration with strong CYP3A4/5 inhibitors (e.g., ketoconazole) significantly increases saxagliptin concentrations. Limit KOMBIGLYZE XR dose to 2.5 mg/1000 mg once daily. (2.2, 7.1)
- Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution. (5.10, 7.2)

USE IN SPECIFIC POPULATIONS

- No adequate and well-controlled studies in pregnant women. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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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.

The onset of lactic acidosis 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.

If acidosis is suspected, KOMBIGLYZE XR should be discontinued and the patient hospitalized immediately [see [Warnings and Precautions \(5.1\)](#)].

1 INDICATIONS AND USAGE

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

1.1 Limitation of Use

KOMBIGLYZE XR should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

KOMBIGLYZE XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using KOMBIGLYZE XR [see [Warnings and Precautions \(5.2\)](#)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The dosage of KOMBIGLYZE XR should be individualized on the basis of the patient's current regimen,

evening meal, with gradual dose titration to reduce the gastrointestinal side effects associated with metformin. The following dosage forms are available:

- KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets 5 mg/500 mg
- KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets 5 mg/1000 mg
- KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets 2.5 mg/1000 mg

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

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

Patients who need 2.5 mg saxagliptin in combination with metformin extended-release may be treated with KOMBIGLYZE XR 2.5 mg/1000 mg. Patients who need 2.5 mg saxagliptin who are either metformin naive or who require a dose of metformin higher than 1000 mg should use the individual components.

The maximum daily recommended dosage is 5 mg for saxagliptin and 2000 mg for metformin extended-release.

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

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

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

The maximum recommended dosage of saxagliptin is 2.5 mg once daily when coadministered with strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). For these patients, limit the KOMBIGLYZE XR dosage to 2.5 mg/1000 mg once daily [see [Dosage and Administration \(2.1\)](#), [Drug Interactions \(7.1\)](#), and [Clinical Pharmacology \(12.3\)](#)].

2.3 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When KOMBIGLYZE XR is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dosage of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia [see [Warnings and Precautions \(5.9\)](#)].

3 DOSAGE FORMS AND STRENGTHS

- KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) 5 mg/500 mg tablets are light brown to brown, biconvex, capsule-shaped, film-coated tablets with “5/500” printed on one side and “4221” printed on the reverse side, in blue ink.
- KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) 5 mg/1000 mg tablets are pink, biconvex, capsule-shaped, film-coated tablets with “5/1000” printed on one side and “4223” printed on the reverse side, in blue ink.
- KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) 2.5 mg/1000 mg tablets are pale yellow to light yellow, biconvex, capsule-shaped, film-coated tablets with “2.5/1000” printed on one side and “4222” printed on the reverse side, in blue ink.

4 CONTRAINDICATIONS

KOMBIGLYZE XR 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.
- Hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to KOMBIGLYZE XR or saxagliptin, such as anaphylaxis, angioedema, or exfoliative skin conditions [*see [Warnings and Precautions \(5.13\)](#) and [Adverse Reactions \(6.2\)](#)*].

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 KOMBIGLYZE XR; when it occurs, it 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 (>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 >5 $\mu\text{g/mL}$ are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/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 insufficiency, 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, in particular those with unstable or acute congestive heart failure

who are at risk of hypoperfusion and hypoxemia, 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 and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. 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. 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 disease. Patients should be cautioned against excessive alcohol intake when taking metformin since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure [*see [Warnings and Precautions \(5.3, 5.6, 5.7, 5.11\)](#)*].

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. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur [*see [Warnings and Precautions \(5.12\)](#)*]. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal 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 [*See [Warnings and Precautions \(5.8\)](#)*].

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 hydrochloride 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 \(4\)](#) and [Warnings and Precautions \(5.6, 5.7, 5.10, 5.11, 5.12\)](#)*].

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