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.

- **Post-marketing 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 >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 KOMBIGLYZE XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (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 used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1.1)

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)
- Assess renal function prior to initiation of KOMBIGLYZE XR and periodically thereafter. (2.3)
  - Do not use in patients with eGFR below 30 mL/min/1.73 m^2.
  - Initiation is not recommended in patients with eGFR between 30 - 45 mL/min/1.73 m^2.
  - Assess risk/benefit of continuing if eGFR falls below 45 mL/min/1.73 m^2.
  - Limit the saxagliptin component to 2.5 mg daily if eGFR is less than 45 mL/min/1.73 m^2.
  - Discontinue if eGFR falls below 30 mL/min/1.73 m^2.
- KOMBIGLYZE XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.4)

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

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2). (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:* See boxed warning. (5.1)
- *Pancreatitis:* If pancreatitis is suspected, promptly discontinue KOMBIGLYZE XR. (5.2)
- *Heart Failure:* Consider the risks and benefits of KOMBIGLYZE XR in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.3)
- *Vitamin B_{12} Deficiency:* Metformin may lower vitamin B_{12} levels. Measure hematological parameters annually. (5.4, 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. (5.6, 6.1)
- *Hypersensitivity-Related Events (e.g., urticaria, facial edema)*: More common in patients treated with saxagliptin than in patients treated with placebo; and post-marketing 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. (5.7, 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. (5.8)
- *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 KOMBIGLYZE XR (5.9).
- *Macrovascular Outcomes*: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR. (5.10)

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-naive 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)
- Carbonic anhydrase inhibitors may increase the risk of lactic acidosis. Consider more frequent monitoring. (7.2)
- 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. (7.3)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.4)

USE IN SPECIFIC POPULATIONS

- *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: 6/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LACTIC ACIDOSIS

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

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

• Post-marketing 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 (> 5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >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 KOMBIGLYZE XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [*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 is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

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, effectiveness, and tolerability. KOMBIGLYZE XR should generally be administered once daily with the 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 Recommendations for Dosing and Administration in Renal Impairment

Assess renal function prior to initiation of KOMBIGLYZE XR and periodically thereafter.

KOMBIGLYZE XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.

Initiation of KOMBIGLYZE XR in patients with an eGFR between 30 – 45 mL/minute/1.73 m^2 is not recommended.

In patients taking KOMBIGLYZE XR whose eGFR later falls below 45 mL/minute/1.73 m^2, assess the benefit risk of continuing therapy and limit dose of the saxagliptin component to 2.5 mg once daily.

Discontinue KOMBIGLYZE XR if the patient's eGFR later falls below 30 mL/minute/1.73 m^2 [*see Contraindications (4) and Warnings and Precautions (5.1)*].

2.4 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue KOMBIGLYZE XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; a history of liver disease, alcoholism or heart failure; or in any patient who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart KOMBIGLYZE XR if renal function is stable [*see Warnings and Precautions (5.1)*].

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:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2).
- 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 (5.7) and Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 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.

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