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 HCl extended-release) tablets
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)**

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

Indications and Usage	
Important Limitations of Use (1.1)	11/2011
Contraindications (4)	11/2011
Warnings and Precautions	
Pancreatitis (5.2)	11/2011
Hypersensitivity Reactions (5.13)	11/2011

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

KOMBIGLYZE XR is a dipeptidyl peptidase-4 (DPP4) inhibitor and biguanide combination product 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)

Important limitations of use:

- Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1.1)
- Has not been studied in combination with insulin. (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 dose based on effectiveness and tolerability. (2.1)
- Do not exceed a daily dose of 5 mg saxagliptin/2000 mg metformin HCl extended-release. (2.1)
- Swallow whole. Never crush, cut, or chew. (2.1)
- Limit the saxagliptin dose 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 not recommended in hepatic impairment and contraindicated in renal impairment. Ensure normal renal function 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)
- There have been postmarketing reports of acute pancreatitis in patients taking saxagliptin. If pancreatitis is suspected, promptly discontinue KOMBIGLYZE XR. (5.2)
- Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Measure hematological parameters annually. (5.5, 6.1)
- Hypoglycemia: When used with an insulin secretagogue (e.g., sulfonylurea), a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia. (5.9)
- There have been postmarketing reports of serious hypersensitivity reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions in patients treated with saxagliptin. In such cases, promptly discontinue KOMBIGLYZE XR, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.13, 6.2)
- Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR or any other antidiabetic drug. (5.14)

----------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.
- Hypersensitivity-related events (e.g., urticaria, facial edema) were reported more commonly in patients treated with saxagliptin than in patients treated with placebo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 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)
- Safety and effectiveness have not been established in children. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 Important Limitations 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 combination with insulin.

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 Dosing

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 dose 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 dose 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 Strong CYP3A4/5 Inhibitors

The maximum recommended dose 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 dose to 2.5 mg/1000 mg once daily. [See *Dosage and Administration (2.1)*, *Drug Interactions (7.1)*, and *Clinical Pharmacology (12.3)*.]

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.

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