

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)

INDICATIONS AND USAGE

KOMBIGLYZE XR is a dipeptidyl peptidase-4 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)

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)

- Temporarily discontinue in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials. (4, 5.1, 5.10)

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 for surgical procedures necessitating restricted intake of food and fluids. (4, 5.1, 5.2, 5.3, 5.6, 5.9)
- Vitamin B₁₂ deficiency: Metformin may lower vitamin B₁₂ levels. Measure hematological parameters annually. (5.4, 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. (5.8)
- Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR or any other antidiabetic drug. (5.12)

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.
- 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. (5.9, 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 FDA-approved patient labeling

Revised: 11/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LACTIC ACIDOSIS

1 INDICATIONS AND USAGE

- 1.1 Important Limitations of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosing
- 2.2 Strong CYP3A4/5 Inhibitors

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Lactic Acidosis
- 5.2 Assessment of Renal Function
- 5.3 Impaired Hepatic Function
- 5.4 Vitamin B₁₂ Concentrations
- 5.5 Alcohol Intake
- 5.6 Surgical Procedures
- 5.7 Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes
- 5.8 Use with Medications Known to Cause Hypoglycemia
- 5.9 Concomitant Medications Affecting Renal Function or Metformin Disposition

- 5.10 Radiologic Studies with Intravascular Iodinated Contrast Materials

- 5.11 Hypoxic States

- 5.12 Macrovascular Outcomes

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

- 7.1 Strong Inhibitors of CYP3A4/5 Enzymes
- 7.2 Cationic Drugs
- 7.3 Use with Other Drugs

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology

14 CLINICAL STUDIES

14.1 Coadministration of Saxagliptin with Metformin
Immediate-Release in Treatment-Naive Patients
14.2 Addition of Saxagliptin to Metformin Immediate-Release

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Instructions

* 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.

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.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.