DPP-4 Inhibitors: ONGLYZA® (saxagliptin)

KOMBIGLYZE® XR (saxagliptin and metformin HCl extended-release) tablets

Our Type 2 Diabetes Portfolio »

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kombiglyze XR (saxagliptin and metformin HCl extended-release) tablets

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Important Safety Information for KOMBIGLYZE XR

WARNING: LACTIC ACIDOSIS
Lactic acidosis is a rare, but serious, complication that can occur...Read More due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake,...Read More...Read More hepatic impairment, renal impairment, and acute congestive heart failure.

A TREATMENT FOR ADULTS WITH TYPE 2 DIABETES MELLITUS, IN ADDITION TO DIET AND EXERCISE
KOMBIGLYZE XR IS NOT INDICATED FOR PATIENTS WITH TYPE 1 DIABETES MELLITUS OR DIABETIC KETOACIDOSIS

Give them a KOMBIGLYZE XR

When your patients need powerful A1C reductions right from the start

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DOSING
INFORMATION

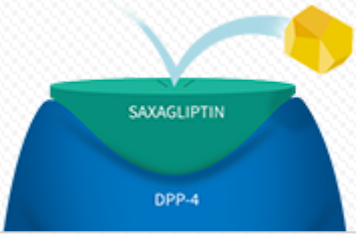
LEARN MORE »

PATIENT
SAVINGS

LEARN MORE »

MECHANISM
OF ACTION

Learn how KOMBIGLYZE XR improves glycemic control by combining saxagliptin and metformin[1]



FORMULARY
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Important Safety Information for KOMBIGLYZE XR

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*]

Contraindications

- Renal impairment (eg, serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women, or abnormal creatinine clearance)
- Hypersensitivity to metformin hydrochloride
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis

angioedema, or exfoliative skin conditions)

Warnings and Precautions

Lactic Acidosis:

- The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases/1000 patient-years). When it occurs, it is fatal in approximately 50% of cases. Reported cases of lactic acidosis have occurred primarily in diabetic patients with significant renal insufficiency
- 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
- Lactic acidosis risk increases with the degree of renal dysfunction and patient age. The risk may be significantly decreased by use of minimum effective dose of metformin and regular monitoring of renal function. Careful renal monitoring is particularly important in the elderly. KOMBIGLYZE XR should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced
- Withhold KOMBIGLYZE XR in the presence of any condition associated with hypoxemia, dehydration, or sepsis

Pancreatitis: There have been postmarketing reports of acute pancreatitis in patients taking saxagliptin, and in the SAVOR cardiovascular outcomes trial after initiating saxagliptin. After initiating KOMBIGLYZE XR, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue KOMBIGLYZE XR and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while using KOMBIGLYZE XR.

Heart Failure: In SAVOR, a cardiovascular outcomes trial enrolling participants with established or multiple risk factors for atherosclerotic cardiovascular disease (ASCVD), more patients treated with saxagliptin were hospitalized for heart failure compared to placebo. Patients with a prior history of heart failure or renal impairment had a higher risk for hospitalization for heart failure. Consider the risks and benefits of KOMBIGLYZE XR in patients who have known risk factors for heart failure. Monitor for signs and symptoms. If heart failure develops, initiate appropriate management and consider discontinuation of KOMBIGLYZE XR.

Renal Function: Before initiation of KOMBIGLYZE XR, and at least annually thereafter, renal function should be assessed and verified as normal.

Impaired Hepatic Function: KOMBIGLYZE XR is not recommended in patients with hepatic impairment.

Vitamin B12 concentrations: Metformin may lower vitamin B12 levels. Measure hematological parameters annually.

Alcohol Intake: Warn patients against excessive alcohol intake.

Surgical Procedures: KOMBIGLYZE XR should be suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids), and should not be restarted until patient's oral intake has resumed and renal function is normal.

- Saxagliptin: When saxagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of confirmed hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia when used in combination with KOMBIGLYZE XR
- Metformin: Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, during concomitant use with other glucose-lowering agents (such as sulfonylureas or insulin), or with use of ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects

Radiological Studies with Iodinated Contrast Materials: Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. KOMBIGLYZE XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours after the procedure and reinstituted only after renal function is normal.

Hypersensitivity: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with saxagliptin, including anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with saxagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue KOMBIGLYZE XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. Use caution in patients with a history of angioedema to another DPP-4 inhibitor as it is unknown whether they will be predisposed to angioedema with KOMBIGLYZE XR.

Arthralgia: There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR or any other anti-diabetic drug.

Adverse Reactions

- Adverse reactions reported in >5% of patients treated with metformin extended-release and more commonly than in patients treated with placebo were: diarrhea (9.6% vs 2.6%) and nausea/vomiting (6.5% vs 1.5%)
- Adverse reactions reported in ≥5% of patients treated with saxagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (7.7% vs 7.6%), urinary tract infection (6.8% vs 6.1%), and headache (6.5% vs 5.9%)
- Adverse reactions reported in ≥5% of treatment-naïve patients treated with coadministered saxagliptin and metformin immediate-release (IR) and more commonly than in patients treated with metformin IR alone were: headache (7.5% vs 5.2%) and nasopharyngitis (6.9% vs 4.0%)

- Confirmed hypoglycemia was reported more commonly in patients treated with saxagliptin 5 mg compared to placebo in the add-on to insulin (with or without metformin) trial (5.3% and 3.3%, respectively). Among the patients using insulin with metformin, the incidence of confirmed hypoglycemia was 4.8% with saxagliptin vs 1.9% with placebo. Confirmed hypoglycemia was reported more commonly with saxagliptin 5 mg compared to placebo in the add-on to metformin plus sulfonylurea trial (1.6% and 0.0%, respectively)

Drug Interactions

- Because ketoconazole, a strong CYP3A4/5 inhibitor, increased saxagliptin exposure, limit KOMBIGLYZE XR to 2.5 mg/1000 mg once daily when coadministered with a strong CYP3A4/5 inhibitor (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin)

Use in Specific Populations

- **Pregnant and Nursing Women:** There are no adequate and well-controlled studies in pregnant women. KOMBIGLYZE XR should be used during pregnancy only if clearly needed. It is not known whether saxagliptin or metformin are secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when KOMBIGLYZE XR is administered to a nursing woman
- **Pediatric Patients:** Safety and effectiveness of KOMBIGLYZE XR in pediatric patients have not been established

Indication and Limitations of Use

- 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
- KOMBIGLYZE XR is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis

Please see US Full Prescribing Information for KOMBIGLYZE XR (5/500•5/1000•2.5/1000 mg tablets), including **Boxed WARNING** about lactic acidosis, and Medication Guide.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.1-800-FDA-1088.

Reference:

1. KOMBIGLYZE XR [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2016.

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