KOMBIGLYZE™ XR (Saxagliptin and Metformin HCl Extended-Release) Tablets Approved in the U.S. for the Treatment of Type 2 Diabetes Mellitus in Adults

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The first and only once-a-day metformin extended-release (XR) plus DPP-4 inhibitor combination tablet

PRINCETON, N.J. & LONDON--(BUSINESS WIRE) -- Bristol-Myers Squibb Company (NYSE: BMY) and AstraZeneca (NYSE: AZN) today announced that the U.S. Food and Drug Administration (FDA) approved KOMBIGLYZE™ XR for the treatment of type 2 diabetes in adults. KOMBIGLYZE XR is the first and only once-a-day metformin extended-release (XR) plus dipeptidyl peptidase-4 (DPP-4) inhibitor combination tablet offering strong glycemic control across glycosylated hemoglobin levels (HbA1c), fasting plasma glucose (FPG) and post-prandial glucose (PPG).

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 should not be used for patients with type 1 diabetes or diabetic ketoacidosis and has not been studied in combination with insulin. Consistent with the Prescribing Information (PI) for metformin alone, the PI for KOMBIGLYZE XR contains a boxed warning for lactic acidosis, a rare, but serious metabolic complication that can occur due to metformin accumulation during treatment with KOMBIGLYZE XR.

Once-a-day KOMBIGLYZE XR combines saxagliptin (also known as ONGLYZA™), a DPP-4 inhibitor, and metformin XR, a biguanide, in one tablet for the treatment of type 2 diabetes. KOMBIGLYZE XR should generally be administered once a day with the evening meal, with gradual dose titration to reduce the gastrointestinal side effects associated with metformin. The maximum daily recommended dose is 5 mg for saxagliptin and 2,000 mg for metformin extended-release.

"Nearly half of adult patients remain uncontrolled on their current treatment regimen and may thus require additional medications," said Elliott Sigal, M.D., Ph.D, executive vice president, chief scientific officer, and president, Research & Development, Bristol-Myers Squibb. "With our heritage of bringing metformin -- the most widely prescribed oral antidiabetic medication -- and more recently saxagliptin to patients in the U.S., we are committed to making KOMBIGLYZE XR the newest building block in our long-term commitment to helping adult patients with type 2 diabetes."

"Patients with type 2 diabetes in the United States can be taking four or five medications for various diseases and conditions, which can lead to complicated medication schedules," said Howard Hutchinson, M.D., chief medical officer, AstraZeneca. "KOMBIGLYZE XR combines two effective diabetes medications in a simple once-a-day dose for adult patients who need A1c reductions."

The Centers for Disease Control and Prevention (CDC) estimate that approximately one in every 11 adults in the United States has diagnosed diabetes. Type 2 diabetes accounts for approximately 90 to 95% of all cases of diagnosed diabetes in adults.

The co-administration of saxagliptin and metformin has been well-studied in adult patients with type 2 diabetes inadequately controlled on metformin alone and in treatment-naive patients inadequately controlled on diet and exercise alone. There have been no clinical efficacy or safety studies conducted with KOMBIGLYZE XR. Relative bioavailability between KOMBIGLYZE XR and coadministered saxagliptin and metformin immediate-release (IR) tablets has not been conducted.

The FDA approved once-a-day KOMBIGLYZE XR based on two Phase III clinical trials and bioequivalence studies. The two clinical studies evaluated the efficacy and safety of saxagliptin and metformin IR as separate tablets compared to placebo added to metformin IR. Bioequivalence was demonstrated in healthy adults between KOMBIGLYZE XR and saxagliptin plus metformin IR as separate tablets.

KOMBIGLYZE XR is contraindicated in patients with renal impairment, metabolic acidosis including diabetic ketoacidosis, and hypersensitivity to metformin. KOMBIGLYZE XR should be temporarily discontinued in patients undergoing radiologic studies with iodinated contrast materials.

KOMBIGLYZE XR Delivered Strong Glycemic Control

A total of 1,306 treatment-naive adult patients with type 2 diabetes participated in a multicenter, randomized, double-blind, active-controlled, 24-week study to evaluate the efficacy and safety of KOMBIGLYZE XR in patients with inadequate glycemic control on diet and exercise alone. KOMBIGLYZE XR, administered as ONGLYZA (saxagliptin) 5 mg and metformin IR
as separate tablets (n=306; baseline HbA1c 9.4%), delivered significant reductions in HbA1c of -2.5% compared to -2.0% with metformin IR plus placebo (n=313; baseline HbA1c 9.4%). In the study, KOMBIGLYZE XR delivered statistically significant reductions in FPG and PPG versus metformin IR plus placebo. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 7.5% with ONGLYZA 5 mg plus metformin IR and 10.1% with metformin IR plus placebo. There was no increase of reported hypoglycemia in treatment-naïve patients treated with KOMBIGLYZE XR: incidence of 3.4% for saxagliptin 5 mg plus metformin IR versus 4.0% with metformin IR alone. The adverse reactions occurring in ≥5% of patients treated with saxagliptin 5 mg plus metformin 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%).

A 24-week, randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy and safety of KOMBIGLYZE XR in 743 adult patients with type 2 diabetes inadequately controlled on metformin monotherapy. This study showed that patients taking KOMBIGLYZE XR, administered as ONGLYZA 5 mg (saxagliptin) and metformin IR as separate tablets (n=186; baseline HbA1c 8.1%), experienced significant reductions in HbA1c of -0.7% compared to an increase of +0.1% in patients taking metformin IR plus placebo (n=175; baseline HbA1c 8.1%). HbA1c reduction with ONGLYZA 2.5 mg plus metformin IR (n=186; baseline HbA1c 8.1%) was -0.6% versus metformin IR plus placebo. In the study, KOMBIGLYZE XR delivered statistically significant reductions in FPG and PPG versus metformin IR plus placebo. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 15% in the ONGLYZA 2.5 mg add-on to metformin IR group, 13% in the ONGLYZA 5 mg add-on to metformin IR group and 27% in the placebo add-on to metformin IR group. The incidences of reported hypoglycemia in patients treated with KOMBIGLYZE XR who were inadequately controlled on metformin were 5.8% for saxagliptin 5 mg plus metformin IR and 7.8% for saxagliptin 2.5 mg plus metformin IR versus 5.0% with metformin IR alone.

KOMBIGLYZE XR Combines Complementary Mechanisms of Action

KOMBIGLYZE XR addresses three key defects in type 2 diabetes, by incorporating the mechanism of saxagliptin, a DPP-4 inhibitor, with metformin, a commonly used glucose lowering agent. With the two active components, saxagliptin and metformin, KOMBIGLYZE XR has a comprehensive mechanism of action that targets and addresses all three key defects in type 2 diabetes for improved glycemic control: increases insulin secretion in a glucose-dependent manner, decreases hepatic glucose production, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

"Type 2 diabetes is a chronic, progressive and multi-factorial disease, and over time, patients often require more than one medication to address the multiple defects associated with the disease," said Matthew Mintz, M.D., FACP, The George Washington University School of Medicine. "KOMBIGLYZE XR now provides patients with the first once-a-day DPP-4 inhibitor and metformin XR combination tablet containing two complementary therapies that can improve key measures of glucose control including glycosylated hemoglobin levels, fasting plasma glucose and postprandial glucose, in a convenient once-a-day treatment regimen."

Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia if used in combination with KOMBIGLYZE XR. 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.

Impact on Body Weight and Gastrointestinal (GI) Adverse Events

As clinicians select various medications to add to the treatment regimens of patients with uncontrolled type 2 diabetes, it is important to consider issues such as weight gain and gastrointestinal disturbances.

Decrease in body weight in the treatment groups given KOMBIGLYZE XR was similar to that in the groups given metformin IR alone.

In patients treated with KOMBIGLYZE XR, diarrhea was the only gastrointestinal-related event that occurred in greater than or equal to 5% in any treatment group. In patients treated with KOMBIGLYZE XR who were inadequately controlled on metformin alone, the incidence of diarrhea was 5.8% (saxagliptin 5 mg plus metformin IR), 9.9% (saxagliptin 2.5 mg plus metformin IR), and 11.2% (metformin IR alone); the incidence in treatment-naïve patients was 6.9% (saxagliptin 5 mg plus metformin IR) and 7.3% (metformin IR alone).

Indication and Important 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 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.

Important Safety 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]

Contraindications

- Renal impairment (e.g., 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
- KOMBIGLYZE XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials because use of such products may result in acute alteration of renal function.

Warnings and Precautions

- 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.
- Before initiation of KOMBIGLYZE XR, and at least annually thereafter, renal function should be assessed and verified as normal.
- KOMBIGLYZE XR is not recommended in patients with hepatic impairment.
- Metformin may lower vitamin B12 levels. Measure hematological parameters annually.
- Warn patients against excessive alcohol intake.
- 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.
- Use of saxagliptin or metformin with medications known to cause hypoglycemia
  - Saxagliptin: Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia if 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.
- 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.
- 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-naive 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%).

**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 (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, neflunivir, 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.

Please click here for US Full Prescribing Information for KOMBIGLYZE XR (5/500•5/1000•2.5/1000 mg tablets), including Boxed WARNING about lactic acidosis

**Bristol-Myers Squibb and AstraZeneca Collaboration**

Bristol-Myers Squibb and AstraZeneca entered into a collaboration in January 2007 to enable the companies to research, develop and commercialize select investigational drugs for type 2 diabetes. The Bristol-Myers Squibb/AstraZeneca Diabetes collaboration is dedicated to global patient care, improving patient outcomes and creating a new vision for the treatment of type 2 diabetes.

**About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit www.bms.com or follow us on Twitter at http://twitter.com/bmsnews.

**About AstraZeneca**

AstraZeneca is a global, innovation-driven biopharmaceutical business with a primary focus on the discovery, development and commercialization of prescription medicines. As a leader in gastrointestinal, cardiovascular, neuroscience, respiratory and inflammation, oncology and infectious disease medicines, AstraZeneca generated global revenues of $32.8 billion in 2009. In the United States, AstraZeneca is a $14.8 billion healthcare business.

For more information about AstraZeneca in the US or our AZ&Me™ Prescription Savings programs, please visit: www.astrazeneca-us.com or call 1-800-AZandMe (292-6363).

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**Language:**

English

**Contact:**

Media:  
Ken Dominski, Bristol-Myers Squibb, 609-252-5251, ken.dominski@bms.com  
Corey Windett, AstraZeneca, 302-885-0034, corey.windett@astrazeneca.com  

or

Investors:  
John Elicker, Bristol-Myers Squibb, 609-252-4611, john. elicker@bms.com  
Karl Hard, AstraZeneca, +44-20-7604-8123, karl.j.hard@astrazeneca.com  
Clive Morris, AstraZeneca, +44-20-7604-8124, clive.morris@astrazeneca.com

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