KOMBIGLYZE™ XR (Saxagliptin and Metformin HCl Extended-Release) Tablets, a New Treatment for Type 2 Diabetes Mellitus in Adults, Now Available in U.S. Pharmacies

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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 KOMBIGLYZE™ XR (saxagliptin and metformin HCl extended-release), approved by the U.S. Food and Drug Administration (FDA) on November 5, 2010, is now available by prescription in pharmacies across the United States. 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.

“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 (saxagliptin and metformin HCl extended-release) 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.”

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.

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.

Indication and Important Limitations of Use for KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets

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 (saxagliptin and metformin HCl extended-release) 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 (saxagliptin and metformin HCl extended-release) 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 (saxagliptin and metformin HCl extended-release) to 2.5 mg/1000 mg once daily when coadministered with a strong CYP3A4/5 inhibitor (e.g., 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.

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).

KOMBIGLYZE XR is a trademark of the Bristol-Myers Squibb Company.