U.S. Food and Drug Administration Approves ONGLYZA™ (saxagliptin) for the Treatment of Type 2 Diabetes Mellitus in Adults

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New Treatment Option for Adult Patients with Inadequate Glucose Control

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 ONGLYZA™ (saxagliptin), a dipeptidyl peptidase-4 (DPP4) inhibitor. ONGLYZA is indicated as an adjunct to diet and exercise to improve blood sugar (glycemic) control in adults for the treatment of type 2 diabetes mellitus. ONGLYZA once daily can be used in combination with commonly prescribed oral anti-diabetic medications – metformin, sulfonylureas or thiazolidinediones (TZD) – or as a monotherapy to significantly reduce glycosylated hemoglobin (A1C) levels. ONGLYZA should not be used for the treatment of type 1 diabetes or for the treatment of diabetic ketoacidosis (high levels of certain acids, known as ketones, in the blood or urine). ONGLYZA has not been studied in combination with insulin.

Nearly Half of All Adult Patients with Type 2 Diabetes Remain Uncontrolled on Their Current Therapy

“The FDA approval of ONGLYZA is an important development for adult patients with type 2 diabetes struggling every day to control their blood sugar levels. 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. “Our ongoing clinical trial program has demonstrated that ONGLYZA showed improved A1C control both in combination and monotherapy settings.”

“Type 2 diabetes is a daily challenge for adult patients and physicians. With the FDA approval of ONGLYZA, physicians and adult patients with type 2 diabetes have an important new treatment to help improve glucose control,” said David Brennan, chief executive officer, AstraZeneca. “ONGLYZA is the product of a major collaboration between AstraZeneca and Bristol-Myers Squibb to further the understanding of how best to treat this challenging disease and help adult patients achieve their treatment goals.”

ONGLYZA™ (saxagliptin) Clinical Development Program

The approval is based on a clinical development program, which included approximately 5,000 individuals, more than 4,000 of whom received ONGLYZA. As part of the development program, ONGLYZA, with diet and exercise, was studied as add-on therapy with other oral anti-diabetic medications, including metformin, the sulfonylurea glyburide and TZDs; in adult patients new to diabetes therapy starting metformin and ONGLYZA together; and as a monotherapy. Throughout the Phase III development program, treatment with ONGLYZA at all doses produced clinically relevant and statistically significant reductions in all three key measures of glucose control studied – A1C, fasting plasma glucose (FPG) and post-prandial glucose (PPG) – when partnered with other commonly used oral anti-diabetic agents (metformin, sulfonylureas and TZDs), or when used as a monotherapy. ONGLYZA was weight and lipid neutral compared to placebo.

ONGLYZA Provides A1C Control Through Effects on Both FPG and PPG

Incretin hormones help the body regulate glucose levels in response to meals by influencing the pancreatic secretion of insulin and glucagon. ONGLYZA increases and prolongs the action of incretin hormones by inhibiting the DPP4 enzyme that inactivates incretins usually within minutes. The inhibition of the DPP4 enzyme by ONGLYZA results in an increase in the production of insulin and a decrease in the production of glucagon by the pancreas. These effects are glucose dependent and enhance the body’s natural response to food to reduce blood sugar levels before and after meals.

“I continue to see adult patients in my practice who, despite treatment, still have high FPG or high PPG, both of which are key contributors to elevated A1C,” said Robert Henry, M.D., Chief, Endocrinology & Metabolism, University of California, San Diego. “The approval of saxagliptin provides a new treatment for adult patients with type 2 diabetes that helps to reduce A1C levels by working across key glucose measures to improve glycemic control.”

ONGLYZA Complements Metformin to Provide Statistically Significant A1C Reductions

ONGLYZA was studied extensively with metformin, the most commonly-prescribed oral anti-diabetic medication. In adult patients inadequately controlled on metformin, the addition of ONGLYZA 2.5 mg (n=192, baseline A1C 8.1 percent) and 5 mg
(n=191, baseline A1C 8.1 percent) once daily reduced A1C levels from baseline to Week 24 by -0.6 percent and -0.7 percent respectively for ONGLYZA™ (saxagliptin) vs. +0.1 percent increase for placebo (p<0.0001 vs. placebo, n=179, baseline A1C 8.1 percent). The reported incidence of hypoglycemia in ONGLYZA 2.5 mg and 5 mg compared with placebo was 7.8 percent, 3.8 percent and 5 percent, respectively.

For those new to diabetes medications, the use of ONGLYZA 5 mg with metformin (n=320, baseline A1C 9.4 percent) as initial therapy lowered A1C from baseline to week 24 by -2.5 percent vs. -2 percent for metformin plus placebo (p<0.0001, n=313, baseline A1C 9.4 percent). Significantly more adult patients in the ONGLYZA plus metformin arm achieved the American Diabetes Association recommended A1C level of less than 7 percent than those treated with metformin plus placebo (60 percent vs. 41 percent, respectively, p<0.05). The reported incidence of hypoglycemia was 3.4 percent in adult patients given ONGLYZA 5 mg plus metformin and 4 percent in adult patients given metformin alone. The adverse reactions occurring in ≥5 percent of adult patients and more commonly than in adult patients treated with metformin alone were headache (7.5 percent vs. 5.2 percent) and nasopharyngitis (6.9 percent vs. 4 percent).

**Complementary and Statistically Significant A1C Reductions When Added to the Sulfonylurea Glyburide or TZDs**

ONGLYZA also offered better glucose control for adult patients currently uncontrolled on glyburide. The addition of ONGLYZA 2.5 mg (n=248, baseline A1C 8.4 percent) or 5 mg (n=253, baseline A1C 8.5 percent) to a submaximal total daily dose of glyburide 7.5 mg reduced A1C levels from baseline at week 24 by -0.5 percent and -0.6 percent, respectively for ONGLYZA vs. +0.1 percent increase with an approximate doubling of the total daily dose of the glyburide plus placebo (p<0.0001 vs. uptitrated glyburide, n=267, baseline A1C 8.4 percent). The reported incidence of hypoglycemia for ONGLYZA 2.5 mg or 5 mg compared with the high-dose glyburide group was 13.3 percent and 14.6 percent vs. 10.1 percent, respectively. Confirmed hypoglycemia was 2.4 percent, 0.8 percent and 0.7 percent, respectively (defined as symptoms of hypoglycemia accompanied by a fingerstick glucose value of ≤50 mg/dL). When used with a sulfonylurea, a lower dose of the sulfonylurea may be required to reduce the risk of hypoglycemia.

When used in addition to TZDs (pioglitazone or rosiglitazone), ONGLYZA™ (saxagliptin) offered additional glucose control. The addition of ONGLYZA 2.5 mg (n=195, baseline A1C 8.3 percent) and 5 mg (n=186, baseline A1C 8.4 percent) reduced A1C levels from baseline at week 24 by -0.7 percent and -0.9 percent, respectively vs. -0.3 percent for placebo (p<0.05 vs. placebo, n=184, baseline A1C 8.2 percent). The reported incidence of hypoglycemia with ONGLYZA 2.5 mg and 5 mg compared with placebo was 4.1 percent and 2.7 percent vs. 3.8 percent, respectively. The incidence of peripheral edema was 3.1 percent and 8.1 percent vs. 4.3 percent as compared to placebo; none resulted in discontinuation of therapy.

**ONGLYZA Provides Significant A1C Reduction When Used as Monotherapy**

When studied as a monotherapy, ONGLYZA significantly improved glucose control, with a difference in A1C from baseline of -0.4 percent and -0.5 percent for ONGLYZA 2.5 mg (n=102, baseline A1C 7.9 percent) and 5 mg (n=106, baseline A1C 8.0 percent), respectively, vs. +0.2 percent increase for placebo (p<0.0001 vs. placebo, n=95, baseline A1C 7.9 percent) at Week 24. The reported incidence of hypoglycemia in the ONGLYZA groups compared with placebo given as monotherapy was 4 percent and 5.6 percent vs. 4.1 percent, respectively.

**ONGLYZA had an Overall Incidence of Side Effects Similar to Placebo**

In clinical trials, the overall incidence of side effects for ONGLYZA 2.5 mg and 5 mg was similar to placebo (72 percent and 72.2 percent vs. 70.6 percent, respectively). The most common events reported with ONGLYZA 5 mg (≥5 percent and more commonly than placebo) were upper respiratory tract infection (7.7 percent vs. 7.6 percent, respectively), urinary tract infection (6.8 percent vs. 6.1 percent, respectively) and headache (6.5 percent vs. 5.9 percent, respectively). In adult patients treated with ONGLYZA 2.5 mg, only headache (6.5 percent) was reported at ≥5 percent and more commonly than in adult patients treated with placebo. Discontinuation of therapy due to adverse events occurred in 2.2 percent, 3.3 percent, and 1.8 percent of patients receiving ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. There was a dose-related mean decrease in absolute lymphocyte count observed with ONGLYZA.

**ONGLYZA™ (saxagliptin) Offers Convenient Once Daily Dosing**

ONGLYZA offers convenient, once-daily dosing of 2.5 mg or 5 mg that can be taken regardless of meals.

ONGLYZA 2.5 mg is recommended for adult patients with moderate or severe renal impairment, or end-stage renal disease requiring hemodialysis (creatinine clearance less ≤50 mL/min). ONGLYZA has not been studied in patients undergoing peritoneal dialysis. Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter.

The dose for ONGLYZA should be limited to 2.5 mg when coadministered with strong cytochrome P450 3A4/5 (CYP 3A4/5) inhibitors (e.g., ketoconazole).

No dose adjustment is required based on gender, race, weight or hepatic impairment.

**IMPORTANT INFORMATION ABOUT ONGLYZA**

**Indication and Important Limitations of Use**

ONGLYZA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

ONGLYZA has not been studied in combination with insulin.

**Important Safety Information**

- **Use With Medications Known to Cause Hypoglycemia**: Insulin secretagogues, such as sulfonylureas, cause
hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA.

- **Macrovascular Outcomes**: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA™ (saxagliptin) or any other antidiabetic drug.

**Most common adverse reactions** (regardless of investigator assessment of causality) reported in ≥5 percent of patients treated with ONGLYZA™ and more commonly than in patients treated with control were upper respiratory tract infection (7.7 percent, 7.6 percent), headache (7.5 percent, 5.2 percent), nasopharyngitis (6.9 percent, 4.0 percent) and urinary tract infection (6.8 percent, 6.1 percent). When used as add-on combination therapy with a thiazolidinedione, the incidence of peripheral edema for ONGLYZA 2.5 mg, 5 mg, and placebo was 3.1 percent, 8.1 percent and 4.3 percent, respectively.

**Drug Interactions**: Because ketoconazole, a strong CYP 3A4/5 inhibitor, increased saxagliptin exposure, the dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP 3A4/5 inhibitor (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, neflinavir, ritonavir, saquinavir, and telithromycin).

**Patients with Renal Impairment**: The dose of ONGLYZA is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease requiring hemodialysis (creatinine clearance ≤50 mL/min). ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis. Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter.

**Pregnant and Nursing Women**: There are no adequate and well-controlled studies in pregnant women. ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

**Pediatric Patients**: Safety and effectiveness of ONGLYZA™ (saxagliptin) in pediatric patients have not been established.

**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 extend and enhance human life. For more information, visit [www.bms.com](http://www.bms.com).

**About AstraZeneca**

AstraZeneca is a major international healthcare business engaged in the research, development, manufacturing and marketing of prescription medicines and supplier for healthcare services. AstraZeneca is one of the world's leading pharmaceutical companies with healthcare sales of US$ 31.6 billion and is a leader in gastrointestinal, cardiovascular, neuroscience, respiratory, oncology and infectious disease medicines. For more information about AstraZeneca, please visit: [www.astrazeneca.com](http://www.astrazeneca.com)

ONGLYZA is a trademark of the Bristol-Myers Squibb Company.


Please see accompanying US Full Prescribing Information or visit [www.bms.com](http://www.bms.com).

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