AstraZeneca United States

AstraZeneca completes acquisition of diabetes alliance assets in the U.S. from Bristol-Myers Squibb

Monday, 3 February 2014

AstraZeneca (NYSE: AZN) today announced that on February 1, 2014, it completed its acquisition of the entirety of Bristol-Myers Squibb's interests in the companies' diabetes alliance. The acquisition gives AstraZeneca ownership of the intellectual property and global rights for the development, manufacture and commercialization of the diabetes business, which in the U.S. includes ONGLYZA® (saxagliptin), KOMBIGLYZE™ XR (saxagliptin and metformin HCl extended release), FARXIGA™ (dapagliflozin), BYETTA® (exenatide), BYDUREON® (exenatide extended-release for injectable suspension), Symlin® (pramlintide acetate) and the investigational agent metreleptin.

On completion of the acquisition, AstraZeneca paid Bristol-Myers Squibb $2.7 billion for initial consideration. AstraZeneca has also agreed to pay up to $1.4 billion in regulatory, launch and sales payments, and various sales-related royalty payments up until 2025, $600 million of which relates to the approval of FARXIGA in the U.S. In addition, AstraZeneca may make payments up to $225 million when certain assets are subsequently transferred.

The transaction reinforces AstraZeneca's long-term commitment to patients with diabetes, a core strategic area and an important platform for returning AstraZeneca to growth.

"AstraZeneca is firmly committed to working closely with healthcare providers and the diabetes community to address the diverse medical needs of the 25.8 million patients living with diabetes in the U.S.," said Paul Hudson, President, AstraZeneca US and Executive Vice President, North America. "Under one leadership, this acquisition will enable AstraZeneca to maximize the potential and expedite progress of our innovative portfolio of non-insulin antidiabetic medicines."

INDICATION and IMPORTANT SAFETY INFORMATION for ONGLYZA® (saxagliptin) tablets

Indication and Limitations of Use for ONGLYZA:

ONGLYZA (saxagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

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

Important Safety Information for ONGLYZA (saxagliptin)**:**

Contraindications

- History of a serious hypersensitivity reaction to ONGLYZA (saxagliptin) (eg, anaphylaxis, angioedema, or exfoliative skin conditions)

Warnings and Precautions

- **Pancreatitis**: There have been postmarketing reports of acute pancreatitis in patients taking ONGLYZA (saxagliptin). After initiating ONGLYZA, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue ONGLYZA and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while using ONGLYZA.
- **Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin**: When ONGLYZA 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 ONGLYZA.
- **Hypersensitivity Reactions**: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with ONGLYZA, including anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with ONGLYZA, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue ONGLYZA, 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 ONGLYZA.
- **Macrovascular Outcomes**: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug.

Most Common Adverse Reactions

- Most common adverse reactions reported in ≥5% of patients treated with ONGLYZA (saxagliptin) and more commonly than in patients treated with control were upper respiratory tract infection (7.7%, 7.6%), headache (7.5%, 5.2%), nasopharyngitis (6.9%, 4.0%) and urinary tract infection (6.8%, 6.1%).
- 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%, 8.1% and 4.3%, respectively.
- Confirmed hypoglycemia was reported more commonly in patients treated with ONGLYZA 2.5 mg and ONGLYZA 5 mg compared to placebo in the add-on to glyburide trial (2.4%, 0.8% and 0.7%, respectively), with ONGLYZA 5 mg compared to placebo in the add-on to insulin (with or without metformin) trial (5.3% and 3.3%, respectively), with ONGLYZA 2.5 mg compared to placebo in the renal impairment

Drug Interactions

Because ketoconazole, a strong CYP3A4/5 inhibitor, increased saxagliptin exposure, the dose of ONGLYZA (saxagliptin) should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

Use in Specific Populations

- **Patients with Renal Impairment**: The dose of ONGLYZA (saxagliptin) is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease requiring hemodialysis (creatinine clearance [CrCl] ≤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 (saxagliptin) is administered to a nursing woman.
- **Pediatric Patients**: Safety and effectiveness of ONGLYZA in pediatric patients have not been established.

Please click here for US Full Prescribing Information for ONGLYZA (saxagliptin) 2.5 mg and 5 mg tablets and click here for Medication Guide.

INDICATION and IMPORTANT SAFETY INFORMATION for KOMBIGLYZE™ XR (saxagliptin and metformin HCl extended-release) tablets

Indication and Limitations of Use for KOMBIGLYZE XR:

KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) 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 patients with a history of pancreatitis.

Important Safety Information for KOMBIGLYZE XR:

BOXED 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

somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, KOMBIGLYZE XR (saxagliptin and metformin HCI extended-release) 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
- History of a serious hypersensitivity reaction to KOMBIGLYZE XR (saxagliptin and metformin HCI extended-release) or saxagliptin (eg, anaphylaxis, angioedema, or exfoliative skin conditions)

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 (saxagliptin and metformin HCI extended-release) 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.
- There have been postmarketing reports of acute pancreatitis in patients taking 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 (saxagliptin and metformin HCI extended-release).
- 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.

- 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.
- Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin
    - 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.
- 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 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 (saxagliptin and metformin HCI extended-release), 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.
- 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

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