Current Agreements

Dealdoc

Asset purchase agreement for diabetes joint venture

AstraZeneca
Bristol-Myers Squibb

Dec 19 2013

Asset purchase agreement for diabetes joint venture

Companies:	AstraZeneca Bristol-Myers Squibb
Announcement date:	Dec 19 2013
Amendment date:	Feb 03 2014
Deal value, US$m:	4100 : sum of upfront and milestone payments
Related contracts:	Joint venture agreement for diabetes Co promotion agreement for dapagliflozin

Details

Announcement date:	Dec 19 2013
Amendment date:	Feb 03 2014
Industry sectors:	Bigpharma
Brand name:	ONGLYZA, KOMBIGLYZE XR, FARXIGA, BYETTA, BYDUREON, Symlin
Compound name:	saxagliptin, saxagliptin and metformin, dapagliflozin, exenatide, exenatide, pramlintide acetate, metreleptin
Asset type:	Business
Therapy areas:	Metabolic » Diabetes
Technology types:	Small molecules
Deal components:	Asset purchase
Stages of development:	Marketed
Geographic focus:	North America » United States

Financials

Deal value, US$m:	4100 : sum of upfront and milestone payments
Upfront, US$m:	2700 : sum of upfront payment
Milestones, US$m:	1400 : regulatory and sales-related milestone payments
Royalty rates, %:	n/d : sales-related royalty payments up until 2025

Termsheet

03 February 2014

AstraZeneca 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.

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.

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.

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19 December 2013

AstraZeneca has agreed to buy Bristol-Myers Squibb's stake in the companies' diabetes joint venture for up to $4.1 billion in a deal.

AstraZeneca would pay Bristol an initial $2.7 billion plus up to $1.4 billion in additional regulatory and sales-related payments.

The decision to quit research and now sell out of the joint venture marks a strategic reversal by Bristol.

Press Release

03 February 2014

AstraZeneca Completes Acquisition of Diabetes Alliance Assets in the U.S. from Bristol-Myers Squibb

WILMINGTON, Del.--(BUSINESS WIRE)--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.

"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."

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.

ONGLYZA has not been studied in patients with a history of pancreatitis.

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 trial (4.7% and 3.5%, respectively), and with ONGLYZA 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, 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 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 (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. • 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. • 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 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 (saxagliptin and metformin HCI extended-release) 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 (saxagliptin and metformin HCI extended-release) 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 (saxagliptin and metformin HCI extended-release) (5/500*5/1000*2.5/1000 mg tablets), including Boxed WARNING about lactic acidosis, and click here for Medication Guide.

INDICATION AND LIMITATION OF USE FOR FARXIGA™ (dapagliflozin)

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

FARXIGA is not recommended for patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION FOR FARXIGA

Contraindications • History of a serious hypersensitivity reaction to FARXIGA (dapagliflozin) • Severe renal impairment, end stage renal disease, or patients on dialysis

Warnings and Precautions • Hypotension: FARXIGA (dapagliflozin) causes intravascular volume contraction. Symptomatic hypotension can occur after initiating FARXIGA, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m2), elderly patients, or patients on loop diuretics. Before initiating FARXIGA in patients with one or more of these characteristics, assess and correct volume status. After initiating therapy, monitor for signs and symptoms of hypotension. • Impairment in Renal Function: FARXIGA (dapagliflozin) increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Adverse reactions related to renal function can occur after initiating FARXIGA. Before initiating FARXIGA, evaluate renal function and monitor periodically thereafter. Discontinue FARXIGA when eGFR is persistently <60 mL/min/1.73 m2. • Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. FARXIGA can increase the risk of hypoglycemia when combined with these agents. Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with FARXIGA. • Genital Mycotic Infections: FARXIGA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately. • Increases in Low-Density Lipoprotein Cholesterol (LDL-C): Increases in LDL-C occur with FARXIGA. After initiating FARXIGA, monitor LDL-C and treat per standard of care. • Bladder cancer: Across 22 clinical studies, newly diagnosed cases of bladder cancer were reported in 0.17% of FARXIGA-treated patients and 0.03% of placebo/comparator-treated patients. After excluding patients in whom exposure to study drug was <1 year at the time of diagnosis of bladder cancer, there were 4 cases with FARXIGA and no cases with placebo/comparator. Bladder cancer risk factors and hematuria (a potential indicator of pre-existing tumors) were balanced between treatment arms at baseline. There were too few cases to determine whether the emergence of these events is related to FARXIGA.

There are insufficient data to determine whether FARXIGA has an effect on pre-existing bladder tumors. FARXIGA should not be used in patients with active bladder cancer. Use with caution in patients with a prior history of bladder cancer. • Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with FARXIGA or any other antidiabetic drug.

Adverse Reactions • In a pool of 12 placebo-controlled studies, the most common adverse reactions (≥5%) treated with FARXIGA (dapagliflozin) 5 mg, 10 mg, and placebo respectively were female genital mycotic infections (8.4% vs 6.9% vs 1.5%), nasopharyngitis (6.6% vs 6.3% vs 6.2%), and urinary tract infections (5.7% vs 4.3% vs 3.7%).

Use in Specific Populations • Pregnant Women: There are no adequate and well-controlled studies of FARXIGA (dapagliflozin) in pregnant women. Consider appropriate alternative therapies, especially during the second and third trimesters. • Nursing Mothers: It is not known whether FARXIGA is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from FARXIGA, discontinue nursing or discontinue FARXIGA. • Geriatric Use: A higher proportion of patients ≥65 years treated with FARXIGA had adverse reactions related to volume depletion and renal impairment or failure compared to patients treated with placebo. No FARXIGA dose change is recommended based on age.

Please click here for US Full Prescribing Information and click here for Medication Guide for FARXIGA (dapagliflozin) 5 mg and 10 mg tablets.

INDICATION and IMPORTANT SAFETY INFORMATION for BYETTA® (exenatide) Injection

Indication and Important Limitations of Use for BYETTA:

BYETTA (exenatide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. • Not a substitute for insulin and should not be used in patients with type 1 diabetes or diabetic ketoacidosis. • Concurrent use with prandial insulin has not been studied and cannot be recommended. • BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, based on postmarketing data. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYETTA; consider other antidiabetic therapies for these patients.

Important Safety Information for BYETTA:

Contraindications • BYETTA (exenatide) is contraindicated in patients with prior severe hypersensitivity reactions to exenatide or to any of the product components.

Warnings and Precautions • Pancreatitis: Based on postmarketing data BYETTA (exenatide) has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation and dose increases of BYETTA, observe patients carefully for pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, with or without vomiting). If pancreatitis is suspected, BYETTA should be discontinued promptly and should not be restarted if pancreatitis is confirmed. • Hypoglycemia: Increased risk of hypoglycemia when used in combination with a sulfonylurea (SU) or when used with a glucose-independent insulin secretagogues (eg, meglitinides). Clinicians may consider reducing the SU dose in patients receiving BYETTA to reduce the risk of hypoglycemia. When used with insulin, evaluate and consider reducing the insulin dose in patients at increased risk of hypoglycemia. • Renal Impairment: Should not be used in patients with severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantation or when initiating or escalating the dose in patients with moderate renal failure. Postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure, and acute renal failure, sometimes requiring hemodialysis and kidney transplantation. •

Gastrointestinal Disease: Because exenatide is commonly associated with gastrointestinal adverse reactions, BYETTA is not recommended in patients with severe gastrointestinal disease (eg, gastroparesis). • Immunogenicity: Patients may develop antibodies to exenatide. In 3 registration trials, antibody levels were measured in 90% of patients, with up to 4% of patients having high-titer antibodies and attenuated glycemic response. If worsening of or failure to achieve adequate glycemic control occurs, consider alternative antidiabetic therapy. • Hypersensitivity: Postmarketing reports of serious hypersensitivity reactions (eg, anaphylaxis and angioedema). If this occurs, patients should discontinue BYETTA and other suspect medications and promptly seek medical advice. • Macrovascular Outcomes: No clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA (exenatide) or any other antidiabetic drug.

Most Common Adverse Reactions (≥5%) • 24-week monotherapy trial vs placebo (PBO): nausea (8% vs 0%). • Three 30-week combination trials of BYETTA (exenatide) added to metformin (MET) and/or SU vs PBO: nausea (44% vs 18%), vomiting (13% vs 4%), and diarrhea (13% vs 6%), feeling jittery (9% vs 4%), dizziness (9% vs 6%), headache (9% vs 6%), dyspepsia (6% vs 3%). • 16-week trial of BYETTA added to thiazolidinedione (TZD) ± MET vs PBO: nausea (40% vs 15%), vomiting (13% vs 1%), dyspepsia (7% vs 1%), diarrhea (6% vs 3%). • 30-week trial of BYETTA added to insulin glargine ± MET and/or TZD vs PBO: nausea (41% vs 8%), vomiting (18% vs 4%), diarrhea (18% vs 8%), headache (14% vs 4%), constipation (10% vs 2%), dyspepsia (7% vs 2%), asthenia (5% vs 1%). • Hypoglycemia: BYETTA as monotherapy vs PBO, 3.8% (10 mcg) and 5.2% (5 mcg) vs 1.3%; BYETTA vs PBO, with metformin (MET): 5.3% (10 mcg) and 4.5% (5 mcg) vs 5.3%; with SU, 35.7% (10 mcg) and 14.4% (5 mcg) vs 3.3%; with MET + SU, 27.8% (10 mcg) and 19.2% (5 mcg) vs 12.6%; with TZD, 10.7% (10 mcg) vs 7.1%; with insulin glargine, 24.8% (10 mcg) vs 29.5%. • Withdrawals: monotherapy trial: 2 of 155 BYETTA patients withdrew due to headache and nausea vs 0 PBO-treated patients. Three 30-week combination trials of BYETTA added to MET and/or SU vs PBO: nausea (3% vs <1%), vomiting (1% vs 0). 16-week trial of BYETTA added to TZD ± MET vs PBO: nausea (9%) and vomiting (5%), with <1% PBO patients withdrawing due to nausea. 30-week trial of BYETTA added to insulin glargine ± MET and/or TZD vs PBO: nausea (5.1% vs 0), vomiting (2.9% vs 0).

Drug Interactions • Oral Medications: BYETTA (exenatide) slows gastric emptying and can reduce the extent and rate of absorption of orally administered drugs. Use with caution with medications that have a narrow therapeutic index or require rapid gastrointestinal absorption. Oral medications dependent on threshold concentrations for efficacy, such as contraceptives or antibiotics, should be taken at least 1 hour before BYETTA. • Warfarin: Postmarketing reports of increased international normalized ratio (INR) sometimes associated with bleeding with concomitant use of warfarin. Monitor INR frequently until stable upon initiation or alteration of BYETTA (exenatide).

Use in Specific Populations • Pregnant and Nursing Women: Based on animal data, BYETTA (exenatide) may cause fetal harm and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To report drug exposure during pregnancy call 1-800-633-9081. When administered to a nursing woman, a decision should be made whether to discontinue nursing or discontinue BYETTA. • Pediatric Patients: Use in pediatric patients is not recommended as safety and effectiveness have not been established.

Please click here for the US full Prescribing Information for BYETTA® (exenatide) injection 5 mcg and 10 mcg, and click here for the Medication Guide.

INDICATION and IMPORTANT SAFETY INFORMATION for BYDUREON® (exenatide extended-release for injectable suspension)

Indication and Important Limitations of Use for BYDUREON:

BYDUREON (exenatide extended-release for injectable suspension) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings. • Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, prescribe only to patients for whom potential benefits are considered to outweigh potential risk. • Not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise. • Not a substitute for insulin, should not be used in patients with type 1 diabetes or diabetic ketoacidosis, and cannot be recommended for use with insulin. • BYDUREON and BYETTA® (exenatide) injection both contain the same active ingredient, exenatide, and should not be used together. • Exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, based on postmarketing data. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYDUREON (exenatide extended-release for injectable suspension); consider other antidiabetic therapies for these patients.

Important Safety Information for BYDUREON:

BOXED WARNING: RISK OF THYROID C-CELL TUMORS

Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON (exenatide extended-release for injectable suspension) causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Contraindications • Patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). • Patients with prior serious hypersensitivity reactions to exenatide or to any of the product components.

Warnings and Precautions • Pancreatitis: Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYDUREON (exenatide extended-release for injectable suspension),

observe patients carefully for pancreatitis (persistent severe abdominal pain, sometimes radiating to the back, with or without vomiting). If pancreatitis is suspected, BYDUREON should be discontinued promptly and should not be restarted if pancreatitis is confirmed. • Hypoglycemia: Increased risk of hypoglycemia when used in combination with a sulfonylurea (SFU). Clinicians may consider reducing the SFU dose to minimize risk of hypoglycemia. It is possible that use of BYDUREON (exenatide extended-release for injectable suspension) with other glucose-independent insulin secretagogues (eg, meglitinides) could increase the risk of hypoglycemia. • Renal Impairment: Should not be used in patients with severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantation or moderate renal failure. Postmarketing reports of altered renal function with exenatide, including increased serum creatinine, renal impairment, worsened chronic renal failure, and acute renal failure, sometimes requiring hemodialysis and kidney transplantation. • Gastrointestinal Disease: Because exenatide is commonly associated with gastrointestinal adverse reactions, BYDUREON is not recommended in patients with severe gastrointestinal disease (eg, gastroparesis). • Immunogenicity: Patients may develop antibodies to exenatide. In 5 registration trials, attenuated glycemic response was associated in 6% of BYDUREON-treated patients with antibody formation. If worsening of or failure to achieve adequate glycemic control occurs, consider alternative antidiabetic therapy. • Hypersensitivity: Postmarketing reports of serious hypersensitivity reactions (eg, anaphylaxis and angioedema). If this occurs, patients should discontinue BYDUREON and other suspect medications and promptly seek medical advice. • Macrovascular Outcomes: No clinical studies establishing conclusive evidence of macrovascular risk reduction with BYDUREON or any other antidiabetic drug.

Withdrawals • In 5 comparator-controlled, 24- to 30-week BYDUREON (exenatide extended-release for injectable suspension) trials, the incidence of withdrawal due to adverse events was 4.9% for BYDUREON, 4.9% for BYETTA, and 2.0% for other comparators. The most common adverse reactions leading to withdrawal for BYDUREON, BYETTA, and comparators respectively were nausea (0.5%, 1.5%, 0.3%), injection-site nodule (0.5%, 0.0%, 0.0%), diarrhea (0.3%, 0.4%, 0.3%), injection-site reaction (0.2%, 0.0%, 0.0%), and headache (0.2%, 0.0%, 0.0%). One percent of BYDUREON patients withdrew due to injection-site adverse reactions.

Most Common Adverse Reactions (≥5%) • BYDUREON (exenatide extended-release for injectable suspension) vs BYETTA (exenatide): ■ 24-week trial: nausea (14% vs 35%), diarrhea (9.3% vs 4.1%), injection-site erythema (5.4% vs 2.4%). ■ 30-week trial: nausea (27% vs 33.8%), diarrhea (16.2% vs 12.4%), vomiting (10.8% vs 18.6%), injection-site pruritus (18.2% vs 1.4%), constipation (10.1% vs 6.2%), gastroenteritis viral (8.8% vs 5.5%), gastroesophageal reflux disease (7.4% vs 4.1%), dyspepsia (7.4% vs 2.1%), injection-site erythema (7.4% vs 0.0%), fatigue (6.1% vs 3.4%), headache (6.1% vs 4.8%), injection-site hematoma (5.4% vs 11.0%).

• BYDUREON vs titrated insulin glargine: nausea (12.9% vs 1.3%), headache (9.9% vs 7.6%), diarrhea (9.4% vs 4.0%), injection-site nodule (6.0% vs 0.0%). • Combination trial vs sitagliptin and pioglitazone: nausea (24.4% vs 9.6% and 4.8%), diarrhea (20.0% vs 9.6% and 7.3%), vomiting (11.3% vs 2.4% and 3.0%), headache (9.4% vs 9.0% and 5.5%), constipation (6.3% vs 3.6% and 1.2%), fatigue (5.6% vs 0.6% and 3.0%), dyspepsia (5.0% vs 3.6% and 2.4%), decreased appetite (5.0% vs 1.2% and 0.0%), injection-site pruritus (5.0% vs 4.8% and 1.2%). • Monotherapy trial vs sitagliptin, pioglitazone, and metformin: nausea (11.3% vs 3.7%, 4.3%, and 6.9%), diarrhea (10.9% vs 5.5%, 3.7%, and 12.6%), injection-site nodule (10.5% vs 6.7%, 3.7%, and 10.2%), constipation (8.5% vs 2.5%, 1.8%, and 3.3%), headache (8.1% vs 9.2%, 8.0%, and 12.2%), dyspepsia (7.3% vs 1.8%, 4.9%, and 3.3%). • Hypoglycemia: No major hypoglycemia was reported for BYDUREON- or comparator-treated patients in five 24- to 30-week trials. Minor hypoglycemia incidences for BYDUREON vs comparator-treated patients were as follows: 24-week trial vs BYETTA: with SFU, 12.5% vs 11.8%; without SFU, 0.0% for both; 30-week trial vs BYETTA: with SFU, 14.5% vs 15.4%; without SFU, 0.0% vs 1.1%; monotherapy trial vs sitagliptin, pioglitazone, and metformin: 2.0% vs 0.0% (all comparators); combination trial vs sitagliptin and pioglitazone: 1.3% vs 3.0% and 1.2%; vs titrated insulin glargine, with SFU, 20.0% vs 43.9%; without SFU, 3.7% vs 19.1%. • Injection-site reactions were observed more frequently in BYDUREON-treated patients (17.1%) vs patients treated with BYETTA (12.7%), titrated insulin glargine (1.8%), or placebo injection (6.4%-13.0%). Injection-site reactions were observed in 14.2% of antibody-positive patients vs 3.1% of antibody-negative patients, with higher incidence in those with higher-titer antibodies. BYETTA-treated patients had similar incidence between antibody-positive and antibody-negative patients (5.8% vs 7.0%). Small, asymptomatic, subcutaneous injection-site nodules are seen with the use of BYDUREON (exenatide extended-release for injectable suspension).

Drug Interactions • Oral Medications: BYDUREON (exenatide extended-release for injectable suspension) slows gastric emptying and can reduce the rate of absorption of orally administered drugs. Use with caution with oral medications. • Warfarin: Postmarketing reports with exenatide of increased international normalized ratio (INR) sometimes associated with bleeding with concomitant use of warfarin. Monitor INR frequently until stable upon initiation or alteration of BYDUREON.

Use in Specific Populations • Pregnant and Nursing Women: Based on animal data, BYDUREON (exenatide extended-release for injectable suspension) may cause fetal harm and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To report drug exposure during pregnancy call 1-800-633-9081. When administered to a nursing woman, a decision should be made whether to discontinue nursing or to discontinue BYDUREON. • Pediatric Patients: Use in pediatric patients is not recommended as safety and effectiveness have not been established.

Please click here for US Full Prescribing Information for BYDUREON (exenatide extended-release for injectable suspension) 2mg, including Boxed WARNING regarding risk of thyroid C-cell tumors, and click here for the Medication Guide.

INDICATIONS and IMPORTANT SAFETY INFORMATION for Symlin® (pramlintide acetate) Injection

Indications:

Symlin® (pramlintide acetate) is indicated as adjunct treatment in adults with type 1 or type 2 diabetes who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy (with or without a concurrent sulfonylurea agent and/or metformin in type 2 diabetes).

Important Safety Information:

BOXED WARNING: SEVERE HYPOGLYCEMIA

SYMLIN (pramlintide acetate) is used with insulin and has been associated with an increased risk of insulin induced severe hypoglycemia, particularly in patients with type 1 diabetes. When severe hypoglycemia associated with SYMLIN use occurs, it is seen within 3 hours following a SYMLIN injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk.

Contraindications • Known hypersensitivity to SYMLIN (pramlintide acetate) or any of its components, including metacresol • Confirmed diagnosis of gastroparesis • Hypoglycemia unawareness

Warnings

Proper patient selection is critical to safe and effective use of SYMLIN (pramlintide acetate): Review HbA1c, recent blood glucose monitoring data, history of insulin-induced hypoglycemia, current insulin regimen, and body weight before initiation of therapy. Only consider SYMLIN for patients with insulin-using type 2 or type 1 diabetes who fulfill the following criteria: • have failed to achieve adequate glycemic control despite individualized insulin management • are receiving ongoing care under the guidance of a healthcare professional skilled in insulin-use and supported by a diabetes educator

Do NOT consider SYMLIN for patients meeting any of the following criteria: • poor compliance with current insulin regimen • poor compliance with prescribed self-blood glucose monitoring • HbA1c >9% • recurrent severe hypoglycemia requiring assistance during the past 6 months • presence of hypoglycemia unawareness • confirmed diagnosis of gastroparesis • require the use of drugs that stimulate gastrointestinal motility • pediatric patients

Hypoglycemia: SYMLIN (pramlintide acetate) alone does not cause hypoglycemia. However, SYMLIN is indicated to be co-administered with insulin therapy and in this setting SYMLIN increases the risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. Severe hypoglycemia associated with SYMLIN occurs within the first 3 hours following a SYMLIN injection. Serious injuries may occur if severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities. Therefore, when introducing SYMLIN therapy, appropriate precautions need to be taken to avoid increasing the risk for insulin-induced severe hypoglycemia. These precautions include frequent pre- and post-meal glucose monitoring combined with an initial 50% reduction in pre-meal doses of short-acting insulin. The addition of any antihyperglycemic agent such as SYMLIN to an existing regimen of one or more antihyperglycemic agents (e.g., insulin, sulfonylurea), or other agents that can increase the risk of hypoglycemia may necessitate further insulin dose adjustments; closely monitor blood glucose.

Precautions

Never mix SYMLIN (pramlintide acetate) and insulin: Administer as separate injections. Mixing can alter the pharmacokinetics of both products.

Allergy: Local allergies such as redness, swelling, or itching at the site of injection may occur. The incidence of systemic allergic reactions was 5% for SYMLIN plus insulin vs. 4%-5% for placebo plus insulin.

Drug Interactions: SYMLIN slows gastric emptying. Do not administer with drugs that alter gastrointestinal motility (e.g., anticholinergic agents such as atropine) or that slow the intestinal absorption of nutrients (e.g., α-glucosidase inhibitors). SYMLIN (pramlintide acetate) has the potential to delay the absorption of concomitantly administered oral medications; if rapid onset is a critical determinant of effectiveness (such as analgesics), the agent should be administered at least 1 hour prior to or 2 hours after SYMLIN injection.

Pregnant and Nursing Women: No adequate and well controlled studies have been conducted in pregnant women. It is unknown whether SYMLIN is excreted in human milk. SYMLIN should only be used in pregnancy or while nursing if the potential benefit justifies the potential risk.

Adverse Reactions

Most common adverse events reported in ≥ 5% of patients treated with SYMLIN (pramlintide acetate) plus insulin and with greater incidence than in patients treated with placebo plus insulin were: • Type 2 Diabetes: nausea (28% vs. 12%), headache (13% vs. 7%), anorexia (9% vs. 2%), vomiting (8% vs. 4%), abdominal pain (8% vs. 7%), fatigue (7% vs. 4%), dizziness (6% vs. 4%), coughing (6% vs. 4%), pharyngitis (5% vs. 2%). • Type 1 Diabetes: nausea (48% vs. 17%), anorexia (17% vs. 2%), inflicted injury (14% vs. 10%), vomiting (11% vs. 7%), arthralgia (7% vs. 5%), fatigue (7% vs. 4%), allergic reaction (6% vs. 5%), dizziness (5% vs. 4%).

The incidence for severe hypoglycemic adverse events in placebo-controlled trials with SYMLIN plus insulin vs. placebo plus insulin and with greater incidence than in patients treated with placebo plus insulin were: • Type 2 Diabetes: Patient-ascertained severe hypoglycemia at 0-3

months (8.2% vs. 2.1%) and at >3-6 months (4.7% vs. 2.4%). Medically assisted severe hypoglycemia at 0-3 months (1.7% vs. 0.7%).

• Type 1 Diabetes: Patient-ascertained severe hypoglycemia at 0-3 months (16.8% vs. 10.8%) and at >3-6 months (11.1% vs. 8.7%). Medically assisted severe hypoglycemia at 0-3 months (7.3% vs. 3.3%) and at >3-6 months (5.2% vs. 4.3%).

Please click here for US Full Prescribing Information for SYMLIN (pramlintide acetate) 60mcg and 120mcg injection, including Boxed WARNING for severe hypoglycemia, and click here for the Medication Guide.

About Type 2 Diabetes

Diabetes is estimated to affect 25.8 million people in the U.S. and more than 382 million people worldwide. The prevalence of diabetes is projected to reach more than 592 million people worldwide by 2035. Type 2 diabetes accounts for approximately 90-95 percent of all cases of diagnosed diabetes. Type 2 diabetes is a chronic disease characterized by pathophysiologic defects leading to elevated glucose levels. Over time, this sustained hyperglycemia contributes to further progression of the disease. Significant unmet needs still exist, as many patients remain inadequately controlled on their current glucose-lowering regimen.

About AstraZeneca

AstraZeneca is a global, innovation-driven biopharmaceutical business that focuses on the discovery, development and commercialization of prescription medicines, primarily for the treatment of cardiovascular, metabolic, respiratory, inflammation, autoimmune, oncology, infection and neuroscience diseases. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information please visit: www.astrazeneca.com.

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19 December 2013

AstraZeneca to buy Bristol out of diabetes venture for up to $4.1 bln

- AstraZeneca to buy Bristol out for an initial $2.7 bln
- AstraZeneca shares touch new high
- CEO says deal will help return AstraZeneca to growth
- Bristol raises quarterly dividend by 3 pct

By Sarah Young and Ben Hirschler

LONDON, Dec 19 (Reuters) - AstraZeneca has agreed to buy Bristol-Myers Squibb's stake in the companies' diabetes joint venture for up to $4.1 billion in a deal that will help return the group to growth, sending its shares to a new high.

AstraZeneca said on Thursday that it would pay Bristol an initial $2.7 billion plus up to $1.4 billion in additional regulatory and sales-related payments.

The move will bulk up AstraZeneca's thin drug portfolio and give Bristol more funds to invest in other areas, such as cancer, where it is developing promising therapies tapping into the immune system.

Following the announcement shares in AstraZeneca hit an 11-year high in early morning trading before paring earlier gains to trade up 1 percent at 3,595 pence by 0935 GMT.

Speculation that AstraZeneca might look to buy out Bristol was fuelled last month when the U.S.-based company decided to get out of diabetes research.

The decision to quit research and now sell out of the joint venture marks a strategic reversal by Bristol, which only last year bought diabetes specialist Amylin Pharmaceuticals for $5.3 billion and folded its products into the alliance with AstraZeneca.

"Today's announcement reinforces AstraZeneca's long-term commitment to diabetes, a core strategic area for us and an important platform for returning AstraZeneca to growth," Chief Executive Pascal Soriot said in a statement.

Soriot, who took over in October last year, has focused on diabetes as a key area for growth, hoping to tap into rising demand for medicines to deal with an epidemic of the disease, which is closely tied to obesity.

Buying the Bristol stake in the venture will boost his company's sales and profits, even as Soriot continues the long-term quest to improve the pipeline of promising experimental medicines.

"To us this looks a sensible deal," Panmure Gordon analyst Savvas Neophytou said.

"Even with a staged earn-out which could rise to $1.6 billion, the price would appear to be good business particularly as it also includes full rights to Onglyza and dapagliflozin."

For Bristol, the deal means it will become an even more focused specialist drugmaker.

In a separate announcement, Bristol said it would raise its quarterly dividend by about 3 percent starting in the first quarter of next year, resulting in an indicative full-year payout of $1.44 per share. The share price closed on Wednesday at $52.59.

The U.S.-based company, which will continue to receive royalty payments from the diabetes unit through to 2025, forecast that earnings per share in 2014 would be between $1.65 and $1.80, broadly in line with the $1.70 to $1.78 it is forecasting for this year.

Bernstein analyst Tim Anderson said in a research note that a price of $4 billion would imply a multiple of 4.8 times sales for the half of the joint venture that AstraZeneca does not already own.

AstraZeneca said the acquisition, which it will finance from existing cash resources and short-term credit facilities, would be neutral to its core earnings in 2014.

A worse than expected performance by Bydureon, one of the diabetes treatments, prompted AstraZeneca to also say that it would incur a non-core impairment charge of around $1.7 billion.

The Bristol-AstraZeneca diabetes joint venture includes the oral medicines Onglyza, Kombiglyze and Forxiga, as well as the injectable treatments Bydureon and Byetta. Last week the venture received a boost when an advisory panel to the U.S. Food and Drug Administration endorsed its new diabetes pill dapagliflozin.

Filing Data

Not available.

Contract

Not available.