Merck Provides Update on Filing Plans for Omarigliptin, an Investigational DPP-4 Inhibitor for Type 2 Diabetes

Terms:
Company Statements

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KENILWORTH, N.J. -- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the company will not proceed with submitting marketing applications for omarigliptin, an investigational, once-weekly DPP-4 inhibitor, in the United States or Europe. This decision did not result from concerns about the efficacy or safety of omarigliptin. Instead, the company has, for business reasons, decided to focus its development resources on a promising pipeline of late-stage compounds and, in early development, new approaches to diabetes control, while continuing to emphasize its existing portfolio of JANUVIA® (sitagliptin), the most prescribed DPP-4 inhibitor worldwide, and JANUMET® (sitagliptin and metformin HCl). Merck remains committed to omarigliptin in Japan, where it is approved and marketed as MARIZEV®.

“We are proud of the significant contributions we have made to improving care for patients with type 2 diabetes through our portfolio of medicines, including JANUVIA and JANUMET,” said Roger M. Perlmutter, M.D., Ph.D., president, Merck Research Laboratories. “Since diabetes is a chronic, progressive disease, we continue to pursue new treatment options for patients, including ertugliflozin, an investigational SGLT-2 inhibitor that we are developing in collaboration with Pfizer. We are also placing greater emphasis on our early pipeline, which includes GLP-1/glucagon co-agonists, novel insulins, and programs that employ novel mechanisms of action to improve the management of diabetes.”

Indications and Usage for JANUVIA® (sitagliptin) 25 mg, 50 mg and 100 mg tablets

JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. JANUVIA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while taking JANUVIA.

Selected Important Risk Information about JANUVIA®

JANUVIA is contraindicated in patients with a history of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema.

There have been postmarketing reports of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUVIA. After initiating JANUVIA, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue JANUVIA and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while taking JANUVIA.

Assessment of renal function is recommended prior to initiating JANUVIA and periodically thereafter. A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with end-stage renal disease requiring hemodialysis or peritoneal dialysis. Caution should be used to ensure that the correct dose of JANUVIA is prescribed.

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal insufficiency, some of whom were prescribed inappropriate doses of sitagliptin.

When JANUVIA was used in combination with a sulfonylurea or insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

The incidence (and rate) of hypoglycemia based on all reports of symptomatic hypoglycemia were: 12.2% (0.59 episodes/patient-year) for JANUVIA 100 mg in combination with glimepiride (with or without metformin), 1.8% (0.24 episodes/patient-year) for placebo in combination with glimepiride (with or without metformin), 15.5% (1.06 episodes/patient-year) for JANUVIA 100 mg in combination with insulin (with or without metformin), and 7.8% (0.51 episodes/patient-year) for placebo in combination with insulin (with or without metformin).

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with JANUVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA, assess for other potential causes for the event, and institute alternative treatment for diabetes.
Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUVIA®.

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from 1 day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUVIA® or with any other antidiabetic drug.

In clinical studies, the adverse reactions reported, regardless of investigator assessment of causality, in ≥5% of patients treated with JANUVIA as monotherapy and in combination therapy and more commonly than in patients treated with placebo, were upper respiratory tract infection, nasopharyngitis, and headache.

Indications and Usage for JANUMET® (sitagliptin and metformin HCl) 50/500 mg and 50/1000 mg tablets

JANUMET is indicated, as an adjunct to diet and exercise, to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.

JANUMET should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. JANUMET has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while taking JANUMET.

Selected Important Risk Information about JANUMET

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare but serious complication that can occur because of 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 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, JANUMET® should be discontinued and the patient hospitalized immediately [see Warnings and Precautions].

JANUMET is contraindicated in patients with renal impairment (serum creatinine levels greater than or equal to 1.5 mg/dL for men and greater than or equal to 1.4 mg/dL for women or abnormal creatinine clearance); hypersensitivity to metformin hydrochloride; acute or chronic metabolic acidosis, including diabetic ketoacidosis; or history of a serious hypersensitivity reaction to JANUMET or sitagliptin (one of the components of JANUMET), such as anaphylaxis or angioedema.

Temporarily discontinue JANUMET 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. Avoid use in patients with hepatic disease. Temporarily discontinue for intercurrent serious conditions, infection, or surgery.

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis.

Before initiation of JANUMET and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and JANUMET discontinued if evidence of renal impairment is present.

When lactic acidosis occurs, it is fatal in approximately 50% of cases. The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications.

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. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient’s age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis.

There have been postmarketing reports of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUMET®. After initiating JANUMET, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue JANUMET and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while taking JANUMET.

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, when receiving JANUMET.
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. Therefore, in patients in whom any such study is planned, JANUMET should be temporarily discontinued at the time of or before the procedure, withheld for 48 hours subsequent to the procedure, and reinstated only after renal function has been re-evaluated and found to be normal.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET or any other antidiabetic drug.

**Use With Medications Known to Cause Hypoglycemia**

**Sitagliptin**

When sitagliptin was used in combination with a sulfonylurea or insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or insulin. Therefore, patients also receiving insulin or an insulin secretagogue (eg, sulfonylurea) may require a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.

The incidence (and rate) of hypoglycemia based on all reports of symptomatic hypoglycemia were: 16.4% (0.82 episodes/patient-year) for sitagliptin 100 mg in combination with metformin and glimepiride, 0.9% (0.02 episodes/patient-year) for placebo in combination with metformin and glimepiride, 8.2% (0.61 episodes/patient-year) for placebo in combination with metformin and insulin, and 15.3% (0.98 episodes/patient-year) for sitagliptin in combination with metformin and insulin.

Adverse reactions with sitagliptin in combination with metformin and rosiglitazone through Week 18 were: upper respiratory tract infection (sitagliptin, 5.5%; placebo, 5.2%) and nasopharyngitis (6.1%, 4.1%). Through Week 54 they were: upper respiratory tract infection (sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.9% vs. 2.8%). In patients treated with sitagliptin in combination with metformin through Week 54 they were: upper respiratory tract infection (sitagliptin, 5.8%; placebo, 2.6%), nasopharyngitis (9.4%, 5.3%), peripheral edema (6.3%, 4.3%), and headache (6.3% vs. 2.6%).

**Metformin hydrochloride**

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, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects.

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUMET®, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUMET, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUMET.

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from 1 day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause of severe joint pain and discontinue drug if appropriate.

In clinical studies, the most common adverse reactions reported, regardless of investigator assessment of causality, in ≥5% of patients treated with either sitagliptin in combination with metformin or placebo were as follows: diarrhea (7.5% vs. 4.0%), upper respiratory tract infection (6.2% vs. 5.1%), and headache (5.9% vs. 2.8%). In patients treated with sitagliptin in combination with metformin and sulfonylurea or placebo in combination with metformin and sulfonylurea: hypoglycemia (16.4% vs. 0.9%) and headache (6.9% vs. 2.7%). In patients treated with sitagliptin in combination with metformin and insulin or placebo in combination with metformin and insulin: hypoglycemia (15.3% vs. 8.2%). Other adverse events with an incidence of ≥5% included nasopharyngitis for sitagliptin monotherapy and diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache for metformin therapy.

**About Merck**

For 125 years, Merck has been a global health care leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic therapies, and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. For more information, visit www.merck.com and connect with us on Twitter, Facebook, YouTube and LinkedIn.

**Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA**

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the “company”) includes “forward-looking statements” within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company’s management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health
care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company’s 2015 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site (www.sec.gov).

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English