Merck Stands Behind the Safety Profile of JANUVIA® (sitagliptin)

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WHITEHOUSE STATION, N.J., March 14, 2013 - Merck, known as MSD outside the United States and Canada, today issued the following statement in response to a communication from the U.S. Food and Drug Administration (FDA) about a potential safety issue that the FDA is investigating regarding type 2 diabetes medicines called incretin mimetic drugs (http://www.fda.gov/Drugs/DrugSafety/ucm343187.htm). These drugs include GLP-1 analogues and DPP-4 inhibitors such as JANUVIA (sitagliptin).

As noted in the FDA statement:

- “FDA has not reached any new conclusions about safety risks with incretin mimetic drugs. This early communication is intended only to inform the public and health care professionals that the Agency intends to obtain and evaluate this new information.”
- “Further, FDA has not concluded these drugs may cause or contribute to the development of pancreatic cancer.”
- “At this time, patients should continue to take their medicine as directed until they talk to their health care professional, and health care professionals should continue to follow the prescribing recommendations in the drug labels.”

“We are confident in the safety profile of sitagliptin, which is an important medicine to help adults with type 2 diabetes lower their blood sugar levels,” said Michael Rosenblatt, M.D., Chief Medical Officer, Merck. “Merck has reviewed all of the safety data on sitagliptin currently available to us and, based on that review, we find no compelling evidence establishing a causal relationship between the use of sitagliptin and pancreatic cancer. Because nothing is more important to Merck than the safety of our medicines and the people who take them, we will continue to vigorously monitor the safety of sitagliptin in close collaboration with regulatory agencies and scientific experts. Type 2 diabetes is a serious condition. As the FDA said, patients should not stop taking any medicine without speaking to their health care professional.”

As also noted in the FDA statement, the Warnings and Precautions section of the drug labels and the patient Medication Guides for incretin mimetic drugs, including JANUVIA, contain warnings about the risk of acute pancreatitis. The FDA issued a previous safety communication on sitagliptin and pancreatitis in 2009. The safety profile of sitagliptin has been established through an extensive pre-clinical and clinical development program as well as post-marketing surveillance. In more than six years of marketed use, more than 50 million total prescriptions have been dispensed for sitagliptin-containing medicines worldwide. Merck believes that the current product labeling appropriately describes the benefits and risks of sitagliptin-containing medicines to inform prescribing. Healthcare providers should inform their patients of the signs and symptoms of acute pancreatitis and remind them to contact their healthcare provider if these symptoms persist.

Safety information from clinical trials

In 2010, Merck published a thorough analysis of adverse event reports from 19 randomized controlled clinical trials based on data from 10,246 patients who were followed for up to two years: 5,429 of whom took sitagliptin 100 mg daily. In this analysis, the overall rate of pancreatitis in patients taking sitagliptin was low and was the same as the rate for patients who did not take sitagliptin and similar to rates that have been reported in the general diabetic population: 1 per 1000 patient-years in each group.

Since that time, we have continued to actively monitor the safety profile of sitagliptin. Subsequent to the pooled analysis published in 2010, Merck conducted a larger pooled analysis that included data from an additional six randomized controlled clinical studies that enrolled approximately 4,300 patients for a total of more than 14,000 patients. In this updated analysis, there were no differences in the incidence of pancreatitis or pancreatic cancer between patients taking sitagliptin and those who did not take sitagliptin.

In addition, the independent Data and Safety Monitoring Board (DSMB) that is overseeing an additional, long-term randomized clinical study of sitagliptin in more than 14,000 patients (which started in 2008) reviewed data from that study in February 2013. The DSMB did not identify any safety concerns to Merck or recommend any changes to the study.

Information from pre-clinical safety studies

The safety of sitagliptin also is supported by an extensive pre-clinical safety program. This includes studies to assess for potential genotoxicity, which tests the ability of a compound to damage DNA, and carcinogenicity, which tests the ability of a compound to cause tumors, in rodents. The latter are conducted over the lifetime of the animals and have been found to...
be highly predictive of tumor findings in humans. In these studies, sitagliptin was shown not to be genotoxic, and in the carcinogenicity studies conducted at exposures that exceed the clinical exposure of sitagliptin, no adverse effects on the pancreas were observed and sitagliptin was not associated with an increase in the incidence of pancreatic malignancies.

Post-marketing adverse events

Merck actively monitors post-marketing reports we receive about sitagliptin, including those the company has received of pancreatitis and pancreatic cancer, and provides these to regulatory agencies around the world in accordance with each agency's requirements. The existence of post-marketing reports describing this event does not establish the presence of an association with sitagliptin.

Post-marketing events are reported voluntarily from a population of uncertain size, and it is generally not possible to reliably establish the frequency of such events or to establish a causal relationship from these reports. Spontaneous post-marketing adverse events may be caused by underlying disease, genetic condition, the medication, concomitant medications or background event that may occur in the population. The Prescribing Information is the best source of information on the benefits and risks of sitagliptin including post-marketing adverse event reports.

About JANUVIA® (sitagliptin) 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® (sitagliptin)

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 percent (0.59 episodes per patient-year) for JANUVIA 100 mg in combination with glimepiride (with or without metformin), 1.8 percent (0.24 episodes per patient-year) for placebo in combination with glimepiride (with or without metformin), 15.5 percent (1.06 episodes per patient-year) for JANUVIA 100 mg in combination with insulin (with or without metformin), and 7.8 percent (0.51 episodes per patient-year) for placebo in combination with glimepiride (with or without metformin).

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA (sitagliptin), 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, promptly 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 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 greater than or equal to 5 percent 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.

About Merck

Today's Merck is a global healthcare 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 consumer care 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 healthcare through far-reaching policies, programs and partnerships. For more information, visit www.merck.com and connect with us on Twitter, Facebook and YouTube.

Forward-Looking Statement
This news release includes “forward-looking statements” within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of Merck’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; Merck ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of Merck patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

Merck 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 Merck’s 2012 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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