Merck Statement Regarding CHMP Review of Incretin-Based Therapies for Type 2 Diabetes, Including Sitagliptin

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WHITEHOUSE STATION, N.J.--(BUSINESS WIRE)--Merck, known as MSD outside the United States and Canada, issued the following statement regarding the conclusion of the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) review of GLP-1, or incretin-based, therapies, including sitagliptin. The EMA issued a news release today, “Investigation into GLP-1 based diabetes therapies concluded: No new concerns for GLP-1 therapies identified on the basis of available evidence.” The EMA’s full news release is available here.

“Nothing is more important to us than the safety of our medicines and the people who take them. We appreciate the important role that the EMA and its CHMP play in monitoring the safety of medicines in Europe,” said Michael Rosenblatt, M.D., executive vice president and chief medical officer, Merck. “We are confident in the safety profile of sitagliptin, an important medicine to help adults with type 2 diabetes lower their blood sugar levels.”

Earlier this year, the U.S. Food and Drug Administration (FDA) issued a Drug Safety Communication on incretin-based drugs, including sitagliptin. The statement indicated that the FDA has not reached any new conclusions about safety risks with incretin mimetic drugs, and recommended that patients continue to take their medicine as directed until they talk to their health care professional, and that health care professionals continue to follow the prescribing recommendations in the drug labels. The FDA said “it will communicate its final conclusions and recommendations when its review is complete or when the Agency has additional information to report.”

The American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and the International Diabetes Federation (IDF) said that they have reviewed the data available to date and found that there is insufficient information to modify current treatment recommendations. On June 28, the three organizations issued a joint statement, which is available here.

“The efficacy and safety profile of sitagliptin supports its use in a wide range of adult patients with type 2 diabetes,” Rosenblatt said. “We will continue to monitor the safety of sitagliptin in close collaboration with regulatory agencies and scientific experts.”

About 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.

About Merck’s review of the data on the safety profile of sitagliptin

In June, Merck presented data regarding the safety profile of sitagliptin at the National Institutes of Health (NIH) Workshop on Pancreatitis-Diabetes-Pancreatic Cancer in the United States. In that presentation, Merck reviewed the available safety data from the company’s non-clinical studies, data from randomized clinical trials with sitagliptin in more than 14,000 patients, post-marketing data including reports of pancreatic cancer, independent observational studies, and a meta-analysis conducted by an independent academic research group of published clinical trials with DPP-4 inhibitors involving more than 33,000 patients.
Safety information from randomized controlled clinical trial data

Randomized, controlled clinical trials continue to be the gold standard for evaluation of the safety of any medicine. Merck conducted a large pooled analysis that included data from 25 randomized controlled clinical studies that enrolled more than 14,000 patients who were followed for up to two years. In this analysis, which was recently published in Diabetes Therapy, there were no differences in the incidence of pancreatitis or pancreatic cancer between patients taking sitagliptin and those who did not take sitagliptin. There were five reports of pancreatitis/acute pancreatitis in the group treated with sitagliptin and five reports in the group that was not treated with sitagliptin, and there were three reports of pancreatic cancer in the group treated with sitagliptin and three reports in the group that was not treated with sitagliptin. Studies in the pooled analysis were not designed or powered to identify or adjudicate events of pancreatitis or pancreatic cancer, and do not allow for inference on the potential for long-term effects.

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) is the largest randomized controlled clinical study with sitagliptin, with more than 14,000 patients enrolled. This study, which began in 2008, is being led by an independent academic research collaboration between the University of Oxford Diabetes Trials Unit and the Duke University Clinical Research Institute. TECOS continues to be monitored through an independent Data and Safety Monitoring Board (DSMB), which has access to unblinded safety reports. The DSMB most recently reviewed data from TECOS in February 2013 and did not identify any safety concerns to Merck or recommend any changes to the study.

Information from Merck non-clinical safety studies

The safety of sitagliptin is also supported by an extensive non-clinical safety program and none of these studies has shown an association or established a causal relationship between sitagliptin and pancreatitis or pancreatic cancer. The non-clinical program includes FDA-requested studies to assess for carcinogenicity in rodents. These are conducted over the lifetime of the animals, and the absence of tumors in rodent carcinogenicity studies is highly predictive of an absence of human cancer risk. The carcinogenicity studies were conducted using doses that achieved levels of sitagliptin approximately 60 to 70 times higher than the levels of sitagliptin achieved in patients taking the maximum recommended daily adult human dose of sitagliptin (100 mg/day). In these studies, no adverse effects on the pancreas were observed and sitagliptin was not associated with an increase in the incidence of pancreatic malignancies.

About DPP-4 inhibitors

Both DPP-4 inhibitors and GLP-1 analogues are incretin-based treatments; however, DPP-4 inhibitors and GLP-1 analogues have different mechanism of actions. DPP-4 inhibitors enhance the body’s own ability to lower blood sugar levels by increasing the levels of the body’s own active incretins, called GLP-1 and glucose-dependent insulinotropic polypeptide, or GIP. GLP-1 analogues are biological products that act as incretin mimetics by directly stimulating the GLP-1 receptors and have no known effect on GIP.

Selected important risk information about JANUVIA® (sitagliptin), continued

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 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 no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUVIA® (sitagliptin) 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.

Merck 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’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 Merck’s 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).


JANUVIA® is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

1 Current Medical Research & Opinion Vol. 27, No. S3, 2011, 57–64
2 Engel, S. et al. Diabetes Ther. 2013, 4:1

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