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Merck Provides Information on FDA Post-Marketing Requirement for Sitagliptin

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Whitehouse Station, N.J., February 28, 2012 – Merck received a Warning Letter from the U.S. Food and Drug Administration (FDA) relating to JANUVIA (sitagliptin) and JANUMET (sitagliptin/metformin HCl) stating that the Company did not fulfill a post-marketing requirement for a 3-month pancreatic safety study in a diabetic rodent model treated with sitagliptin. The letter was issued by FDA's Office of Scientific Investigations on February 17th.

Merck is fully committed to complying with FDA's requirement and is confident that the Company will complete the requirement within the time frame outlined in the February 17 letter. Specifically, Merck will submit a final protocol for a new rodent study to FDA for review within 30 days of the date of the letter, revise it as necessary to gain FDA's agreement on the new study, and start the study within 6 months. Merck is preparing its response to the FDA now, including the design of the new study.

The post-marketing requirement was included by FDA as part of its February, 2010 approval of supplemental new drug applications for JANUVIA and JANUMET; the required study was to have been completed and submitted to FDA by June 15, 2011.

Merck has been providing information to the FDA on Merck's efforts. These efforts included the submission of a manuscript to the FDA with data from a 12-month study in mice that was conducted by an independent researcher. However, FDA informed Merck that what Merck has submitted does not satisfy the post-marketing requirement, and directed Merck to conduct a new 3-month rodent study.

Merck remains fully committed to completing this requirement. Merck takes its responsibility to comply with FDA regulations very seriously, and is thoroughly reviewing its processes and procedures to ensure that Merck fulfills its commitments to the FDA going forward.

The approval letters with information on the post-marketing requirement are posted on FDA's website:
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021995s010s011s012s014ltr.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022044s010s012s013ltr.pdf

More information about FDA's post-marketing requirements can be found on FDA's website:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm292758.htm

Preliminary data from the 12-month study that Merck submitted to FDA in February were presented at ADA in June, 2011, and final results have been submitted for publication.

Important Information About JANUVIA
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. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. 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.

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.

Important Information About JANUMET
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
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, JANUMET should be discontinued and the patient hospitalized immediately.

JANUMET is contraindicated in patients with renal disease or renal dysfunction (serum creatinine levels ≥1.5 mg/dL in males and ≥1.4 mg/dL in females) or abnormal creatinine clearance; acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma; 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.

Measure renal function before initiation of therapy with JANUMET and periodically thereafter. 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 insufficiency, 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 reinstituted 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 (5.5%, 4.1%).

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. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. 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.

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
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 statement includes "forward-looking statements" within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. Such statements may include, but are not limited to, statements about the benefits of the merger between Merck and Schering-Plough, including future financial and operating results, the combined company's plans, objectives, expectations and intentions and other statements that are not historical facts. Such statements are based upon the current beliefs and expectations of Merck's management and are subject to significant risks and uncertainties. Actual results may differ from those set forth in the forward-looking statements.

The following factors, among others, could cause actual results to differ from those set forth in the forward-looking statements: the possibility that the expected synergies from the merger of Merck and Schering-Plough will not be realized, or will not be realized within the expected time period; the impact of pharmaceutical industry regulation and health care legislation; the risk that the businesses will not be integrated successfully; disruption from the merger making it more difficult to maintain business and operational relationships; Merck's ability to accurately predict future market conditions; dependence on the effectiveness of Merck's patents and other protections for innovative products; the risk of new and changing regulation and health policies in the U.S. and internationally and the exposure to 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 2011 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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