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## Merck Provides Update on Combination Medicine JUVISYNC™ (sitagliptin and simvastatin) Tablets

Thursday, September 26, 2013 8:00 am EDT

Merck, known as MSD outside the United States and Canada, today said that the company will voluntarily discontinue distributing JUVISYNC™ (sitagliptin and simvastatin) tablets to pharmacies and wholesalers in the United States and Puerto Rico. This decision is for business reasons only and is not due to the efficacy or safety profile of JUVISYNC or the individual components. JUVISYNC is a treatment that combines the glucose-lowering medication sitagliptin, the active component of JANUVIA® (sitagliptin), with the cholesterol-lowering medication simvastatin. Sitagliptin and simvastatin will continue to be available as separate medicines.

During their next visit, patients taking JUVISYNC should discuss treatment options with their prescribing physician.

JUVICOR®, the brand name of the sitagliptin/simvastatin combination tablet outside the United States, will continue to be marketed and distributed outside the United States. JUVICOR is currently approved in 10 countries, and Merck plans to continue filing applications in additional countries.

### About JUVISYNC™ (sitagliptin and simvastatin) tablets

JUVISYNC is indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate.

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

Simvastatin is indicated as an adjunct to diet to reduce the risk of total mortality by reducing coronary heart disease (CHD) deaths, the risk of nonfatal myocardial infarction and stroke, and the need for coronary and noncoronary revascularization procedures in patients at high risk of coronary events because of existing CHD, diabetes, peripheral vessel disease, history of stroke, or other cerebrovascular disease. Simvastatin is also indicated as an adjunct to diet to reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hyperlipidemia or mixed dyslipidemia; to reduce elevated TG in patients with hypertriglyceridemia; to reduce elevated TG and VLDL-C in patients with primary dysbetalipoproteinemia; and to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an

JUVISYNC should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, and JUVISYNC 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 for the development of pancreatitis while using JUVISYNC.

JUVISYNC has not been studied in conditions in which the major abnormality is elevation of chylomicrons (i.e., hyperlipidemia Fredrickson types I and V).

Because doses of JUVISYNC appropriate for patients with severe renal impairment or end-stage renal disease (ESRD) are not available in this combination product, JUVISYNC is not recommended in these patients.

### **Selected Important Risk Information About JUVISYNC™ (sitagliptin and simvastatin) tablets**

JUVISYNC is contraindicated in patients with a history of a serious hypersensitivity reaction, such as anaphylaxis or angioedema, to any component of JUVISYNC; in those receiving concomitant administration of strong CYP3A4 inhibitors (eg, itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, and nefazodone), gemfibrozil, cyclosporine, or danazol; or in those with active liver disease. JUVISYNC is also contraindicated in women who are or may become pregnant and nursing mothers. JUVISYNC should be administered to women of childbearing age only when such patients are highly unlikely to conceive.

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

Simvastatin occasionally causes myopathy, manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10 times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. Predisposing factors for myopathy include advanced age ( $\geq 65$  years), female gender, uncontrolled hypothyroidism, and renal impairment. The risk of myopathy, including rhabdomyolysis, is dose related. All patients starting therapy with JUVISYNC, or whose dose of JUVISYNC is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing JUVISYNC. Therapy with JUVISYNC should be discontinued immediately if markedly elevated CK levels occur or myopathy is diagnosed or suspected.

In addition to the drugs that are contraindicated, because of an increased risk of myopathy/rhabdomyolysis, grapefruit juice should be avoided. Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing JUVISYNC with colchicine.

The dose of simvastatin should not exceed 10 mg (100 mg/10 mg or 50 mg/10 mg JUVISYNC) daily in patients receiving verapamil, diltiazem, or dronedarone, and 20 mg (100 mg/20 mg or 50 mg/20 mg JUVISYNC) daily in patients receiving amiodarone, amlodipine, or ranolazine. The benefits of combined use of JUVISYNC with these drugs, other fibrates, or niacin ( $\geq 1$  g/day) should be carefully weighed against the potential risk of myopathy/rhabdomyolysis. Caution should be used when treating Chinese patients with JUVISYNC 100 mg/40 mg or 50 mg/40 mg per day coadministered with lipid-modifying doses of niacin-containing products.

Persistent increases to more than 3 times the ULN in serum transaminases have occurred in approximately 1 percent of patients who received simvastatin in clinical studies. Liver function tests should be performed before initiating treatment and thereafter when clinically indicated. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with JUVISYNC, promptly interrupt therapy and do not restart unless an alternate etiology is found.

JUVISYNC is not recommended for use in patients with severe renal impairment or ESRD because doses of sitagliptin appropriate for these patients are not available in this combination product. Assessment of renal function is recommended prior to initiation of JUVISYNC™ (sitagliptin and simvastatin) and periodically thereafter.

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

When JUVISYNC is used in combination with a sulfonylurea or insulin, 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/patient-year) for sitagliptin 100 mg in combination with glimepiride (with or without metformin), 1.8 percent (0.24 episodes/patient-year) for placebo in combination with glimepiride (with or without metformin), 15.5 percent (1.06 episodes/patient-year) for sitagliptin 100 mg in combination with insulin (with or without metformin), and 7.8 percent (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 sitagliptin, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JUVISYNC, assess for other potential causes, and institute alternative treatment. 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 JUVISYNC.

Increases in A1C and fasting serum glucose levels have been reported with statins, including simvastatin.

In clinical studies, the adverse reactions reported, regardless of investigator assessment of causality, in >5 percent of patients treated with sitagliptin as monotherapy and in combination therapy and more commonly than in patients treated with placebo, 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%).

In clinical studies, the adverse reactions reported, regardless of investigator assessment of causality, in  $\geq$ 5 percent of patients treated with simvastatin were upper respiratory tract infection (9.0%), headache (7.4%), abdominal pain (7.3%), constipation (6.6%), and nausea (5.4%).

The dosages for therapy with JUVISYNC are 100 mg/10 mg, 100 mg/20 mg, 100 mg/40 mg, 50 mg/10 mg, 50 mg/20 mg, and 50 mg/40 mg (sitagliptin/simvastatin) once daily. The recommended starting dose of JUVISYNC is 100/40 mg once daily in the evening.

## 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](http://www.merck.com) (<http://www.merck.com/>) and connect with us on Twitter (<https://twitter.com/Merck>), Facebook (<http://www.facebook.com/MerckBeWell>) and YouTube (<http://www.youtube.com/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](http://www.sec.gov)) (<http://www.sec.gov>).

The Prescribing Information and Medication Guide for JUVISYNC™ (sitagliptin and simvastatin) are available at

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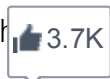
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