New Analyses from the IMPROVE-IT Outcomes Study of VYTORIN® (ezetimibe and simvastatin) and the TECOS Cardiovascular Safety Trial of JANUVIA® (sitagliptin) Will Be Presented at the European Society of Cardiology Congress

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Additional Real-World Analyses from DYSIS and DYSIS II Assessing the Treatment of Dyslipidemia to be Presented

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, announced today that new analyses from the investigational IMPROVE-IT (IMProved Reduction of Outcomes: VYTORIN Efficacy International Trial) study of VYTORIN® (ezetimibe and simvastatin), the TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) cardiovascular safety trial of JANUVIA® (sitagliptin), and real-world data from the Dyslipidemia International Study (DYSIS I and DYSIS II) will be presented at the upcoming European Society of Cardiology (ESC) Congress 2015, held Aug. 29 to Sept. 2, 2015. IMPROVE-IT was designed to evaluate the cardiovascular benefit of the combination of ezetimibe and simvastatin compared to simvastatin alone. The TECOS cardiovascular safety trial was designed to assess the cardiovascular safety of Merck’s DPP-4 inhibitor, JANUVIA. In all, Merck has 13 data presentations at this year’s ESC.

“At this year’s European Society of Cardiology Congress, we are pleased to share new data from two important studies – IMPROVE-IT and the TECOS cardiovascular safety trial – which have already added substantially to our knowledge of cardiovascular disease and the cardiovascular safety profile of sitagliptin, respectively,” said Dr. Roy Baynes, senior vice president, global clinical development, Merck Research Laboratories.

The primary results from IMPROVE-IT, which enrolled 18,144 high-risk patients presenting with acute coronary syndromes (ACS), were presented in November 2014 at the American Heart Association Scientific Sessions and published in The New England Journal of Medicine in June 2015. VYTORIN and ZETIA® (ezetimibe) are indicated for use along with a healthy diet to reduce elevated LDL cholesterol in patients with hyperlipidemia. The current U.S. Prescribing Information for VYTORIN and ZETIA states that the effect of ezetimibe on cardiovascular disease and the cardiovascular safety profile of sitagliptin, respectively, has not been determined. Merck has submitted the data from IMPROVE-IT to regulatory authorities in the U.S. and European Union to support a new indication for reduction of major cardiovascular events for VYTORIN® and ZETIA®.

TECOS was an event-driven study of more than 14,000 patients that evaluated the long-term cardiovascular safety of the addition of JANUVIA to usual care, compared to usual care without JANUVIA, in patients with type 2 diabetes and established cardiovascular disease. The primary results of the TECOS cardiovascular safety trial were presented at the 75th Scientific Sessions of the American Diabetes Association and published simultaneously in the New England Journal of Medicine in June 2015.

Indications and Limitations of Use 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 no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUVIA or with any other antidiabetic drug.
Analysis of DYSIS and DYSIS II

The cross-sectional, observational study DYSIS examined lipid goal attainment among statin-treated patients including patients suffering from coronary heart disease (CHD), diabetes, chronic kidney disease or peripheral atherosclerotic disease. DYSIS enrolled approximately 60,000 patients from 30 countries from regular clinical practice such as physicians’ offices and hospital outpatient wards between 2008 and 2012. DYSIS II, a continuation of DYSIS study evaluating lipid goal attainment, enrolled approximately 4,000 ACS patients and 7,000 CHD patients globally between 2012 and 2014.

The following data will be presented at ESC Congress 2015:

TECOS Cardiovascular Safety Trial Data Analysis

- (Oral Presentation) Trial Evaluating Cardiovascular Outcomes with Sitagliptin in Patients with Type 2 Diabetes: TECOS
  - Monday, Aug. 31: 11:00AM - 12:30PM GMT; Presentation 11:00AM - 11:10AM GMT. Location: London – Main Auditorium, Hot Line III – Diabetes Mellitus/Pharmacology

IMPROVE-IT Data Analysis

- (Oral Presentation) Safety and Efficacy of Long-term Very Low Achieved LDL-C in the IMPROVE-IT Trial
  - Saturday, Aug. 29: 11:00AM - 12:30PM GMT; Presentation 11:20AM - 11:37AM GMT. Location: San Marino – Village 2, Low-Density Lipoprotein Cholesterol: How Low and How To Lower?

- (Moderated Poster) Prospective Evaluation of Cancer in 18,144 Patients Randomized to Ezetimibe vs Placebo: a Prespecified Analysis from the IMPROVE-IT Trial
  - Sunday, Aug. 30: 10:00AM - 11:00AM GMT; Presentation 10:51AM - 11:00AM GMT. Location: Poster Area, Managing Lipids – Statins and Beyond

- (Poster Session) Muscle Related Complaints, Serious Adverse Events and Drug Discontinuations in 17,706 Subjects Randomized to Simvastatin or Ezetimibe/Simvastatin in the IMPROVE-IT Study
  - Tuesday, Sept. 1: 2:00PM - 4:00PM GMT. Location: Poster Area, Surveillance of Risk Factors and Interventions

- (Best Posters) Achievement Of Dual LDL-C (<70 mg/dL) And hs-CRP (<2 mg/L) Goals More Frequent With Addition Of Ezetimibe and Associated With Better Outcomes In IMPROVE-IT
  - Tuesday, Sept. 1: 2:00PM - 4:00PM GMT. Location: Poster Area, Best Posters in Medical Therapy of Stable Coronary Artery Disease

- (Oral Presentation) Incidence of New Onset Diabetes in the IMPROVE-IT Trial: Does Adding Ezetimibe to Simvastatin Increase Risk Compared to Simvastatin Alone?
  - Tuesday, Sept. 1: 2:00PM - 3:30PM GMT; Presentation 2:30PM-2:45PM GMT. Location: Hyde Park – The Hub, Clinical Trial Update III - Pharmacology & Therapy.

- (Oral Presentation) Benefit Of Adding Ezetimibe To Statin Therapy On Cardiovascular Outcomes And Safety In Patients With Vs. Without Diabetes: The IMPROVE-IT Trial
  - Sunday, Aug. 30: 2:00PM - 3:30PM GMT; Presentation 2:15PM – 2:30PM GMT. Location: Hyde Park – The Hub, Clinical Trial Update I - Cardiovascular Diseases: Prevention, Outcomes, Quality.

DYSIS & DYSIS II Data Analysis

- (Poster Session) High Prevalence of Persistent Lipid Abnormalities Among Coronary Patients: The Dyslipidemia International Study (DYSIS) II Global Results
  - Sunday, Aug. 30: 8:30AM – 12:30PM GMT. Location: Poster Area, Treatment Strategies and Adherence: Can We Decrease Risk?

- (Poster Session) Are Coronary Patients on Lipid-lowering Therapy in Europe Achieving the Recommended LDL-C Target? Results from the Dyslipidemia International Study (DYSIS) II Europe
  - Sunday, Aug. 30: 8:30AM – 12:30PM GMT. Location: Poster Area, Strategies and Adherence: Can We Decrease Risk?

- (Poster Session) Prevalence of Lipid Abnormalities Among Coronary Patients Remains High in the Middle East/Africa Region: The Dyslipidemia International Study (DYSIS) II MEA results
  - Sunday, Aug. 30: 8:30AM – 12:30PM GMT. Location: Poster Area, Strategies and Adherence: Can We Decrease Risk?

- (Poster Session) LDL-C Target Attainment Remains Low Among Treated Coronary Patients in Asia-Pacific: The Dyslipidemia International Study (DYSIS) II AP Results
  - Sunday, Aug. 30: 8:30AM – 12:30PM GMT. Location: Poster Area, Strategies and Adherence: Can We Decrease Risk?

- (Poster Session) Unexpected High Prevalence of Possible and Probable FH in Clinical Practice - Results of DYSIS I
  - Sunday, Aug. 30: 8:30AM – 12:30PM GMT. Location: Poster Area, Classical and New Risk Factors for Cardiovascular Disease

- (Oral Presentation) Low LDL-cholesterol Target Achievement in Statin-treated Patients in Clinical Practice in China and Europe: Results of the Dyslipidemia International Study (DYSIS)
  - Saturday, Aug. 29: 11:00AM - 12:30PM GMT; Presentation 11:37AM - 11:54 AM GMT. Location: San Marino - Village 2 - Low-Density Lipoprotein Cholesterol: How Low and How to Lower?

About VYTORIN® (ezetimibe and simvastatin)
VYTORIN contains ezetimibe and simvastatin. VYTORIN is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B, triglycerides, and non-HDL cholesterol, and to increase HDL cholesterol in patients with primary (heterozygous familial and nonfamilial) hyperlipidemia or mixed hyperlipidemia when diet alone is not enough.

The Prescribing Information for VYTORIN states that no incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established. VYTORIN is not indicated to reduce cardiovascular events in patients who have presented with acute coronary syndromes.

VYTORIN (ezetimibe and simvastatin) should not be taken with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erlythromycin, clarithromycin, telithromycin, nefazodone, and cobicistat-containing products); or with gemfibrozil, cyclosporine, or danazol. VYTORIN also should not be taken by anyone with active liver disease, unexplained persistent elevations of hepatic transaminase levels, or hypersensitivity to the product; or by women who are pregnant, nursing or may become pregnant.

Selected cautionary information about VYTORIN

All patients starting therapy with VYTORIN, or whose dose of VYTORIN is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to promptly report any unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing VYTORIN. VYTORIN should be discontinued immediately if markedly elevated creatine kinase (CK) levels occur or myopathy is diagnosed or suspected. VYTORIN contains simvastatin, which occasionally causes myopathy manifested as muscle pain, tenderness, or weakness with CK levels above 10 times 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 (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment. The risk of myopathy, including rhabdomyolysis, is dose related.

The 10/80 mg dose of VYTORIN should not be started in new patients. The risk of myopathy, including rhabdomyolysis, is greater in patients taking simvastatin 80 mg compared with other statin therapies with similar or greater LDL cholesterol lowering efficacy, and with lower doses of simvastatin. The 10/80 mg dose of VYTORIN® should be used only in patients who have been taking that dose chronically (e.g., for 12 months or more) without evidence of muscle toxicity. If a patient who is currently tolerating the 10/80 mg dose needs to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin, that patient should be switched to an alternative statin or statin-based regimen with less potential for the drug-drug interaction. Please read Warnings and Precautions in the Prescribing Information for additional information.

In addition to drugs that are contraindicated because of an increased risk of myopathy/rhabdomyolysis, grapefruit juice should be avoided. Use caution when prescribing VYTORIN with a fenofibrate, and immediately discontinue both drugs if myopathy is diagnosed or suspected. Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be used when prescribing VYTORIN (ezetimibe and simvastatin) with colchicine.

The dose of VYTORIN should not exceed 10/10 mg daily in patients receiving verapamil, diltiazem or dronedarone, and 10/20 mg daily in patients receiving amiodarone, amlopipine or ranolazine. For patients with homzygous familial hypercholesterolemia (HoFH) taking lomitapide, the dose should not exceed 10/20 mg/day (or 10/40 mg/day for patients who have previously taken simvastatin 80 mg/day chronically, e.g., for 12 months or more, without evidence of muscle toxicity); patients initiating lomitapide should have their dose of VYTORIN reduced by 50%. The benefits of combined use of VYTORIN with these drugs, other fenofibrates, or niacin (≥1 g/day) should be carefully weighed against the potential risk of myopathy/rhabdomyolysis. Caution should be used when Chinese patients taking niacin (≥1 g/day) are coadministered doses of VYTORIN exceeding 10/20 mg/day; Chinese patients should not receive VYTORIN 10/80 mg with niacin.

Persistent elevations in hepatic transaminase can occur. Liver function tests should be performed at treatment initiation and thereafter when clinically indicated. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment, therapy should be interrupted promptly and not restarted unless an alternate etiology is found.

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including simvastatin.

In clinical trials, the most commonly reported side effects, regardless of cause, included headache (5.8 percent), increased ALT (3.7 percent), myalgia (3.6 percent), upper respiratory tract infection (3.6 percent), and diarrhea (2.8 percent).

VYTORIN tablets contain ezetimibe and simvastatin: 10 mg of ezetimibe and 10, 20, 40, or 80 mg of simvastatin (VYTORIN 10/10, 10/20, 10/40, or 10/80 mg, respectively). The usual dosage range is 10/10 mg/day to 10/40 mg/day; patients should not be titrated to the restricted 10/80-mg dose.

About ZETIA® (ezetimibe)

ZETIA, administered alone or in combination with a statin, is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B, and non-HDL cholesterol in patients with primary (heterozygous familial and non-familial) hyperlipidemia when diet alone is not enough.

The Prescribing Information for ZETIA states that the effect of ZETIA on cardiovascular morbidity and mortality has not been determined. ZETIA is not indicated for use with a statin to further reduce cardiovascular events in patients who have presented with acute coronary syndromes.

ZETIA (ezetimibe) should not be taken by people with hypersensitivity to any component of the medication. Statin contraindications also apply when ZETIA is used with these drugs: statins are contraindicated in patients with active liver disease, unexplained persistent elevations in hepatic transaminase levels and in pregnant and nursing women. Refer to individual statin labels for details about who should not take that statin.
Selected cautionary information about ZETIA

When using ZETIA with a statin, also follow the label recommendations for that specific statin.

When ZETIA was coadministered with a statin, consecutive elevations in hepatic transaminase levels (greater than or equal to 3 times ULN) were slightly higher (1.3 percent) than those of statins alone (0.4 percent). Liver function tests should be performed when ZETIA is added to statin therapy and according to statin recommendations. Should an increase in ALT or AST greater than or equal to 3 times ULN persist, consider withdrawal of ZETIA and/or the statin.

Patients should be advised to promptly report muscle pain, tenderness, or weakness. Risk for skeletal muscle toxicity increases with higher statin doses, advanced age (>65), hypothyroidism, renal impairment, and depending on the statin used, concomitant use of other drugs. Discontinue drug if myopathy is diagnosed or suspected.

ZETIA is not recommended in patients with moderate to severe hepatic impairment.

The coadministration of ZETIA with fibrates other than fenofibrate is not recommended until use in patients is adequately studied. Exercise caution when using ZETIA and cyclosporine concomitantly because exposure to both drugs is increased. Cyclosporine concentrations should be monitored in these patients.

ZETIA should be used in pregnant or nursing women only if the benefit outweighs the risk.

In clinical trials, regardless of causality assessment, the most frequent side effects for ZETIA® coadministered with a statin versus a statin alone included nasopharyngitis (3.7 percent vs 3.3 percent), myalgia (3.2 percent vs 2.7 percent), upper respiratory tract infection (2.9 percent vs 2.8 percent), arthralgia (2.6 percent vs 2.4 percent), and diarrhea (2.5 percent vs 2.2 percent); for ZETIA administered alone vs placebo: upper respiratory tract infection (4.3 percent vs 2.5 percent), diarrhea (4.1 percent vs 3.7 percent), arthralgia (3.0 percent vs 2.2 percent), sinusitis (2.8 percent vs 2.2 percent), pain in extremity (2.7 percent vs 2.5 percent), and fatigue (2.4 percent vs 1.5 percent).

Selected Important Risk Information about JANUVIA® (continued)

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.

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 (sitagliptin) 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 (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, 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 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 and YouTube.

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 2014 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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