Merck Receives Complete Response Letter from the U.S. FDA for ZETIA® (ezetimibe) and VYTORIN® (ezetimibe and simvastatin)

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KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, announced today that the U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter regarding Merck's Supplemental New Drug Applications for ZETIA® and VYTORIN® for the reduction of the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, or need for revascularization) in patients with coronary heart disease. The applications were based on the results of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial). Merck is reviewing the letter and will determine next steps.

ZETIA and VYTORIN are indicated for use along with a healthy diet to reduce elevated LDL cholesterol in patients with hyperlipidemia. The effect of ZETIA on cardiovascular morbidity and mortality has not been determined. VYTORIN contains 2 active ingredients: ezetimibe and simvastatin. No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

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.

ZETIA 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.

Because renal impairment is a risk factor for statin-associated myopathy, doses of simvastatin exceeding 20 mg should be used with caution and close monitoring when administered concomitantly with ZETIA in patients with moderate to severe renal impairment (eGFR <60 mL/min/1.73 m²).

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

The coadministration of ZETIA (ezetimibe) 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
Risks and uncertainties include but are not limited to, general industry material from those set forth in the forward-looking statements. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

About VYTORIN® (ezetimibe and simvastatin)

VYTORIN contains ezetimibe and simvastatin. VYTORIN is indicated 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.

VYTORIN should not be taken with strong CYP3A4 inhibitors; 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 (ezetimibe and simvastatin)

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. Please read Warnings and Precautions in the Prescribing Information for additional information.

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.

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 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, amiodipine or ranolazine. For patients with homozgyous 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(ezetimibe and simvastatin) reduced by 50 percent. 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. See Dosage and Administration in the Prescribing Information for additional information.

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 partners 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, YouTube and LinkedIn.

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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