



NEWS RELEASE

# New FDA Approved Labeling For VYTORIN® (Ezetimibe/Simvastatin) Includes Results From the Study of Heart and Renal Protection (SHARP) in Patients With Moderate to Severe Chronic Kidney Disease

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--FDA Approves New Labeling for VYTORIN to Include Data From SHARP Showing That VYTORIN Effectively Lowered LDL Cholesterol in These Patients, With Fewer Major Vascular Events in Patients Taking VYTORIN Compared to Placebo

--New Indications not Approved for VYTORIN or ZETIA®(Ezetimibe) Because Independent Contributions of Ezetimibe and Simvastatin Were not Assessed

Merck (NYSE:MRK), known as MSD outside the United States and Canada, announced today that the U.S. Food and Drug Administration (FDA) has approved an updated label for VYTORIN® (ezetimibe/simvastatin) that includes results from the Study of Heart and Renal Protection (SHARP). In SHARP, VYTORIN 10/20 mg lowered LDL cholesterol in patients with moderate to severe chronic kidney disease (CKD), and major vascular events were reduced in the treatment group compared to placebo. The trial therefore demonstrated that treatment with VYTORIN 10/20 mg versus placebo reduced the risk for major vascular events in this CKD population. Because SHARP studied the combination of simvastatin and ezetimibe compared with placebo, it was not designed to assess the independent contributions of each drug to the observed effect; for this reason, the FDA did not approve a new indication for VYTORIN or for ZETIA® (ezetimibe) and the study's efficacy results have not been incorporated into the label for ZETIA.

VYTORIN is indicated as adjunctive therapy to diet for the reduction of 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 contains two 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.

"Merck is committed to supporting clinical research that helps to address important questions in medicine. The results of SHARP as described in the new label for VYTORIN can help the medical community understand the role of lowering lipids with VYTORIN in managing cardiovascular risk in patients with CKD," said Michael Mendelsohn, M.D., senior vice president & head, atherosclerosis and cardiovascular research, Merck Research Laboratories.

VYTORIN should not be taken with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone); with gemfibrozil, cyclosporine, or danazol; 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.

CKD is associated with an increased risk of cardiovascular disease. According to the National Kidney Foundation, patients with CKD should be considered to be at high cardiovascular risk, equivalent to that of patients with coronary heart disease.

SHARP is the first randomized controlled trial involving LDL cholesterol lowering therapy to demonstrate a reduction in cardiovascular outcomes in patients with CKD

SHARP was designed and independently conducted by the Clinical Trial Service Unit (CTSU) of Oxford University (the trial's regulatory sponsor) and CTSU provided the analyses for the FDA. The SHARP trial results were published last June in *The Lancet*. A total of 9,438 patients with chronic kidney disease were enrolled. Approximately one-third of the patients were undergoing dialysis therapy for end-stage renal disease at the time of entry, and the remaining patients were pre-dialysis patients with advanced CKD with a median estimated glomerular filtration rate (GFR, a measure of kidney function) of 25.6 ml/min/1.73m<sup>2</sup>. Patients with a prior history of myocardial infarction or a coronary (heart) revascularization procedure were excluded from the study.

The average baseline LDL cholesterol of all patients enrolled in SHARP was 108 mg/dL. Eligibility did not depend on lipid levels. For the first year of the trial, patients were allocated in a ratio of 4:4:1 to receive VYTORIN 10/20 mg daily, placebo or simvastatin 20 mg alone. After one year, patients initially allocated to simvastatin alone were re-allocated to either VYTORIN 10/20 mg daily or placebo for the remainder of the study period. Patients were

followed for a median of 4.9 years.

The one year simvastatin-only arm enabled comparison of VYTORIN to simvastatin with regard to safety and effect on lipid levels. At one year, compared to placebo, LDL cholesterol was 26 percent lower in patients who received simvastatin and 38 percent lower in patients who received VYTORIN. At the mid-point of the study (2.5 years), the mean LDL cholesterol was 32 percent lower for VYTORIN relative to placebo. Patients no longer taking study medication were included in all lipid measurements.

The primary endpoint for the study was time to first major vascular event, defined as the composite of non-fatal heart attack or cardiac death, stroke or revascularization procedure in the two groups assigned to VYTORIN or placebo at study initiation. (This analysis did not include patients initially randomized to simvastatin alone for the first year.) In the primary intent-to-treat analysis, 639 (15.2 percent) of 4,193 patients initially allocated to VYTORIN and 749 (17.9 percent) of 4,191 patients initially allocated to placebo experienced a major vascular event, which corresponded to a significant ( $p=0.001$ ) relative risk reduction of 16 percent. The SHARP study design precluded drawing conclusions about the independent contribution of either ezetimibe or simvastatin to the observed effect on major vascular events.

The effect of VYTORIN on major vascular events was less among patients on dialysis compared with those not on dialysis. Among 3,023 patients on dialysis at baseline, VYTORIN reduced the risk of major vascular events by 6 percent (relative risk of 0.94, with 95 percent confidence interval of 0.80 to 1.09), compared with 22 percent (relative risk of 0.78, with 95 percent confidence interval of 0.69 to 0.89) among 6,247 patients not on dialysis at baseline.

#### 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. 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 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.

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.

#### Dosing of VYTORIN in patients with renal impairment/CKD

In patients with CKD and GFR <60 mL/min/1.73 m<sup>2</sup>, the dose of VYTORIN is 10/20 mg/day in the evening. In such patients, higher doses should be used with caution and close monitoring.

For other patients, including those with mild renal impairment, the usual dosage range remains 10/10 mg/day to 10/40 mg/day and the recommended usual starting dose is 10/10 mg/day or 10/20 mg/day. In the absence of moderate to severe renal impairment, patients who require a larger reduction in LDL cholesterol (greater than 55%) may be started at 10/40 mg/day. No dosage adjustment is necessary in patients with mild renal impairment (GFR ≥60 mL/min/1.73 m<sup>2</sup>).

VYTORIN is available as tablets containing 10 mg of ezetimibe combined with 10, 20, 40, or 80 mg of simvastatin (VYTORIN 10/10, 10/20, 10/40, or 10/80 mg, respectively). Because the 10/80 mg dose of VYTORIN contains 80 mg of simvastatin, use of that dose is restricted, and patients should not be titrated to 10/80 mg. See Dosage and Administration in the Prescribing Information for additional information.

#### Additional selected cautionary information

In addition to drugs that are contraindicated because of an increased risk of myopathy/rhabdomyolysis, large quantities of grapefruit juice (>1 quart daily) should be avoided. Use of VYTORIN is not recommended with fibrates other than gemfibrozil (which is contraindicated). Dose adjustment of VYTORIN may be needed when used with voriconazole. 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 or diltiazem, and 10/20 mg daily in patients receiving amiodarone, amlodipine or ranolazine. The benefits of combined use of VYTORIN with these drugs, other fibrates, 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.

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, VYTORIN is not recommended in these patients.

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 alanine aminotransferase (ALT) (3.7 percent), myalgia (3.6 percent), upper respiratory tract infection (3.6 percent), and diarrhea (2.8 percent).

Updated renal impairment labeling for ZETIA summarizes information about use with simvastatin in patients with moderate to severe CKD

In addition, sections of the label for ZETIA have been updated to include information based on SHARP about dosing of simvastatin with ZETIA in patients with moderate to severe renal impairment. That label states that, 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. When ZETIA is given alone, no dosage adjustment is necessary in patients with renal impairment. As described above, efficacy data from SHARP that appear in the label for VYTORIN are not included in the label for ZETIA.

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 nonfamilial) hyperlipidemia when diet alone is not enough. The effect of ZETIA on cardiovascular morbidity and mortality has not been determined.

ZETIA should not be taken by people with hypersensitivity to any component of this medication. Statin contraindications apply when ZETIA is used with a statin: active liver disease; unexplained persistent elevations in hepatic transaminase levels. Statins are contraindicated in pregnant and nursing women. Refer to statin label 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 ( $\geq 3 \times$  ULN) were slightly higher (1.3%) 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 aspartate transaminase (AST)  $\geq 3 \times$  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).

## 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) and connect with us on Twitter, Facebook and YouTube.

## 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. 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 United States 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 2010 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)).

Please see Prescribing Information for VYTORIN (ezetimibe/simvastatin) at [www.merck.com/product/usa/pi\\_circulars/v/vytorin/vytorin\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/v/vytorin/vytorin_pi.pdf) and Patient Information for VYTORIN at [www.merck.com/product/usa/pi\\_circulars/v/vytorin/vytorin\\_ppi.pdf](http://www.merck.com/product/usa/pi_circulars/v/vytorin/vytorin_ppi.pdf).

Please see Prescribing Information for ZETIA (ezetimibe) at [http://www.merck.com/product/usa/pi\\_circulars/z/zetia/zetia\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/z/zetia/zetia_pi.pdf) and Patient Information for ZETIA at [http://www.merck.com/product/usa/pi\\_circulars/z/zetia/zetia\\_ppi.pdf](http://www.merck.com/product/usa/pi_circulars/z/zetia/zetia_ppi.pdf).

Merck

Media Contacts:

Pam Eisele, 908-423-5042

Skip Irvine, 267-305-5397

or

Investor Contact:

Carol Ferguson, 908-423-4465