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**Merck/Schering-Plough Pharmaceuticals Comments on
Results of the ENHANCE Study**

**Study Presented at American College of Cardiology Scientific Sessions and
Published in On-Line Version of *The New England Journal of Medicine***

CHICAGO, March 30, 2008 -- Results of ENHANCE (Ezetimibe aNd simvastatin in Hypercholesterolemia enhANCES atherosclerosis rEgression), an imaging trial in 720 patients with heterozygous familial hypercholesterolemia (HeFH), a rare genetic condition that causes very high levels of LDL "bad" cholesterol and greatly increases the risk for premature coronary artery disease, were presented at the 57th annual scientific sessions of the American College of Cardiology and also were published on-line in *The New England Journal of Medicine*ⁱ.

As previously reported on Jan. 14, 2008, despite the fact that ezetimibe/simvastatin 10/80 mg (VYTORIN[®]*) significantly lowered LDL "bad" cholesterol more than simvastatin 80 mg alone, there was no significant difference between treatment with ezetimibe/simvastatin and simvastatin alone on the pre-specified primary endpoint, a change in the thickness of carotid artery walls over two years as measured by ultrasound. There also were no significant differences between treatment with ezetimibe/simvastatin and simvastatin on the four pre-specified key secondary endpoints: percent of patients manifesting regression in the average carotid artery intima-media thickness (CA IMT); proportion of patients developing new carotid artery plaques >1.3 mm; changes in the average maximum CA IMT; and changes in the average CA IMT plus in the average common femoral artery IMT.

In ENHANCE, when compared to simvastatin alone, ezetimibe/simvastatin significantly lowered LDL "bad" cholesterol, as well as triglycerides and C-reactive protein (CRP).

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* VYTORIN includes the two components (ezetimibe and simvastatin) in one tablet. VYTORIN[®] is a trademark of MSP Singapore Company, LLC. All other brands are trademarks of their respective owners and are not trademarks of MSP Singapore Company, LLC.

Ezetimibe/simvastatin is not indicated for the reduction of CRP. In the ENHANCE study, as previously reported, the overall safety profile of ezetimibe/simvastatin in the study was generally consistent with the product label.

“LDL cholesterol remains the primary target of lipid-modifying therapy and physicians should continue to lower patients' elevated LDL cholesterol and get their patients to their goals based on guidelines,” said Michael Davidson, M.D., professor, director of preventive cardiology, The University of Chicago, Pritzker School of Medicine.

In the ENHANCE publication, the authors provided three theoretical explanations why, despite ezetimibe/simvastatin significantly lowering LDL “bad” cholesterol more than simvastatin (56 percent vs. 39 percent, $p < 0.01$), there was no significant difference between treatment groups on the primary endpoint and four key secondary endpoints: (1) lowering of LDL cholesterol with non-statin therapy, such as ezetimibe, might affect IMT differently than statin therapy, (2) the imaging technology selected was not sensitive enough to detect a difference, or (3) that these HeFH patients were extensively pretreated with lipid-lowering therapy, thereby limiting the amount that CA IMT could change with further LDL cholesterol-lowering therapy, consequently limiting the ability to detect a differential response to the two treatments. The authors concluded that the reason for the failure to observe an incremental effect on CA IMT thickness in spite of a reduction of level of LDL cholesterol remains unknown.

In the publication, the authors addressed the premise that the lack of a difference in change of mean CA IMT between ezetimibe/simvastatin and simvastatin despite greater LDL cholesterol-lowering could be attributed to lipid-independent effects of statins on arteries. The authors presented several facts that argued against this concept, including a discussion of clinical studies involving statin and non-statin therapeutic approaches that demonstrated that cardiovascular risk reductions were associated with the degree of LDL-cholesterol lowering. The authors suggested that clinical outcomes data are needed to answer this question.

As for the hypothesis that the results may reflect the imaging technology, the authors noted this seems unlikely given the precision of the imaging measurement results seen in the ENHANCE trial.

With respect to the hypothesis that the ENHANCE results were due to the characteristics of the patients studied, the authors pointed out that in an earlier imaging study (extension of ASAP or **A**torvastatin vs. **S**imvastatin on **A**therosclerosis **P**rogression study) use of potent lipid-lowering therapy in HeFH patients produced “regression” or “thinning” of CA IMT during the first one to two years of therapy, but further decreases during the following two years on the same therapy were not seen. In ENHANCE, approximately 80 percent of the enrolled patients

reported taking statin treatment at the time of screening for the study, and had a mean baseline CA IMT of 0.69 to 0.70 mm. In another recent IMT study in HeFH patients (RADIANCE 1 or **Rating Atherosclerotic Disease Change by Imaging with A New CETP Inhibitor** study), the baseline CA IMT was also lower than in the earlier IMT study and similar to ENHANCE and, importantly, the pattern of change in CA IMT in this IMT study was very similar to that observed in both treatment groups in the ENHANCE study.

The authors noted that "these data raise the possibility that there may be limits to the extent to which the lowering of LDL cholesterol levels can result in a further decrease in the progression of intima-media thickness in the context of previous statin therapy and a modest baseline intima-media thicknessⁱⁱ."

"Although a definitive explanation is never possible with a finding like this, we believe that the most likely explanation for the failure to see a significant difference between treatment groups in ENHANCE relates to the behavior of IMT in this population of HeFH patients," noted Thomas Musliner, M.D., executive director, Cardiovascular Disease, Clinical Research, Merck Research Laboratories. "The large majority of these patients were previously treated with LDL cholesterol-lowering therapy and presumably experienced an effect on CA IMT from that treatment, as reflected in the patients' relatively low CA IMT values when they began the study. The findings of the ASAP extension, RADIANCE 1 and ENHANCE suggest there are limits to how much IMT can be decreased in HeFH study cohorts in the context of the widespread and prolonged use of effective LDL cholesterol-lowering treatment starting at an earlier age, which is now the standard of care for these patients."

Endpoint data and cardiovascular events

ENHANCE investigators found no statistically significant difference between the two treatment groups on the primary endpoint, the change in the average CA IMT at three carotid artery locations. The change from baseline in the mean (average) CA IMT in the ezetimibe/simvastatin group was 0.0111 mm, which did not significantly differ from the simvastatin group's change of 0.0058 mm (P=0.29). The median data for the primary endpoint, which also showed no statistical difference between treatments, was 0.0058 mm in the ezetimibe/simvastatin group and 0.0095 mm for the simvastatin group. The treatment groups also did not have statistically significant differences for each of the three carotid artery locations that comprised the primary endpoint: the common carotid, the internal carotid and the carotid bulb. The data for these analyses, key secondary endpoints and cardiovascular events are included in the attachment.

The ENHANCE study was not designed nor powered to evaluate cardiovascular clinical events. IMPROVE-IT is underway and is designed to provide cardiovascular outcomes data for ezetimibe/simvastatin in patients with acute coronary syndrome. No incremental benefit of ezetimibe/simvastatin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

Lipid parameters of LDL cholesterol, triglycerides and HDL cholesterol; and C-reactive protein

Over the two-year period of the ENHANCE study based upon the "last observation carried forward" endpoint approach, the group treated with ezetimibe/simvastatin had a 56 percent mean reduction of LDL cholesterol (from a baseline of 319 mg/dL) that was significantly greater than the 39 percent mean reduction of LDL cholesterol (from a baseline of 318 mg/dL) in the group treated with simvastatin alone ($P < 0.01$). The LDL cholesterol-lowering observed in patients treated with ezetimibe/simvastatin in the ENHANCE trial was generally consistent with the LDL cholesterol-lowering of ezetimibe/simvastatin seen in separate head-to-head studies vs. simvastatin, vs. Crestor[®] and vs. Lipitor[®].

In addition, by study completion, the ezetimibe/simvastatin group had a 30 percent median reduction in triglycerides (from baseline 157 mg/dL), significantly more than the 23 percent median reduction (from baseline 160 mg/dL) in the simvastatin group ($P < 0.01$). Also, the ezetimibe/simvastatin group had a 49 percent median reduction in CRP (from baseline 1.70 mg/L), significantly more than the 24 percent median reduction in CRP (from baseline 1.70 mg/L) in the simvastatin group ($P < 0.01$). The ezetimibe/simvastatin group had a 10 percent increase (from baseline 46.7 mg/dL) in HDL "good" cholesterol; the simvastatin group had an 8 percent increase from baseline 47.4 mg/dL ($P = 0.05$, no statistical significance).

Safety data

As previously reported, the overall safety profiles of ezetimibe/simvastatin and simvastatin alone were similar and generally consistent with their product labels. Both medicines were generally well tolerated. Also, the overall incidence rates of treatment-related adverse events were 34 percent for ezetimibe/simvastatin (122/357) and 29 percent (107/363) for simvastatin only; the incidence rates for discontinuations due to adverse events were 8.1 percent for ezetimibe/simvastatin (29/357) and 9.4 percent for simvastatin only (34/363). Additional adverse event data are included in the attachment.

About the study design and methodology

The ENHANCE study was an international two-year, randomized, double-blind, controlled trial in 720 HeFH patients between the ages of 30 to 75. All of the ENHANCE patients had HeFH, which affects approximately 0.2 percent of the population. The rationale for studying HeFH patients is that these patients are known to be at increased risk for premature coronary artery disease and, if untreated, exhibit increased IMT progression rates beginning in childhood. Prior LDL cholesterol-lowering therapy of any kind was not an exclusion criterion for ENHANCE, although such therapies were discontinued at the start of the study. Also, there wasn't a minimum value for CA IMT specified for inclusion in study. Following a six-week, single blind, placebo lead-in/drug "wash-out" period, patients were randomized to receive either daily ezetimibe/simvastatin 10/80 mg (N=357) or daily simvastatin 80 mg (N=363).

ENHANCE investigators took digitized single-frame CA IMT images at the three locations of the patients' right and left carotid arteries, the main arteries in the neck that provide blood to the brain. These images were taken at several time points: study baseline, 6, 12, 18 and 24 months.

"Examination of the CA IMT collected during ENHANCE proved to be a far more challenging process than originally anticipated when the study design was drawn up. Therefore, preparation of the images for entry into a database took significantly longer than expected, as the blinded investigators and CA IMT evaluators took numerous steps in 2006 and 2007 to address image quality control and finalize the analysis," said Enrico P. Veltri, M.D., co-author of the ENHANCE study publication and group vice president, Global Clinical Research, Cardiovascular and Metabolic Diseases, Schering-Plough Research Institute. "Our companies acted with integrity and good faith in connection with the trial," he said.

Important information about VYTORIN

Ezetimibe/simvastatin is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL cholesterol, Apo B, triglycerides and non-HDL cholesterol and to increase HDL cholesterol in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia.

Ezetimibe/simvastatin is also indicated for the reduction of elevated total cholesterol and LDL cholesterol in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Ezetimibe/simvastatin is a prescription medicine and should not be taken by people who are hypersensitive to any of its components. Ezetimibe/simvastatin should not be taken by anyone with active liver disease or unexplained persistent elevations of serum transaminases.

Women who are of childbearing age (unless highly unlikely to conceive), are nursing or who are pregnant should not take ezetimibe/simvastatin.

Selected cautionary information for VYTORIN

Muscle pain, tenderness or weakness in people taking ezetimibe/simvastatin should be reported to a doctor promptly because these could be signs of a serious side effect.

Ezetimibe/simvastatin should be discontinued if myopathy is diagnosed or suspected. To help avoid serious side effects, patients should talk to their doctor about medicine or food they should avoid while taking ezetimibe/simvastatin.

In three placebo-controlled, 12-week trials, the incidence of consecutive elevations (≥ 3 X ULN) in serum transaminases were 1.7 percent overall for patients treated with ezetimibe/simvastatin and 2.6 percent for patients treated with ezetimibe/simvastatin 10/80 mg. In controlled long-term (48-week) extensions, which included both newly-treated and previously-treated patients, the incidence of consecutive elevations (≥ 3 X ULN) in serum transaminases was 1.8 percent overall and 3.6 percent for patients treated with ezetimibe/simvastatin 10/80 mg. These elevations in transaminases were generally asymptomatic, not associated with cholestasis and returned to baseline after discontinuation of therapy or with continued treatment. Doctors should perform blood tests before, and periodically during treatment with ezetimibe/simvastatin when clinically indicated to check for liver problems. People taking ezetimibe/simvastatin 10/80 mg should receive an additional liver function test prior to and three months after titration and periodically during the first year.

Due to the unknown effects of increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ezetimibe/simvastatin is not recommended in these patients. The safety and effectiveness of ezetimibe/simvastatin with fibrates have not been established; therefore, co-administration with fibrates is not recommended. Caution should be exercised when initiating ezetimibe/simvastatin in patients treated with cyclosporine and in patients with severe renal insufficiency.

Ezetimibe/simvastatin has been evaluated for safety in more than 3,800 patients in clinical trials and was generally well tolerated at all doses (10/10 mg, 10/20 mg, 10/40 mg, 10/80 mg). In clinical trials, the most commonly reported side effects, regardless of cause, included headache (6.8 percent), upper respiratory tract infection (3.9 percent), myalgia (3.5 percent), influenza (2.6 percent) and extremity pain (2.3 percent).

About Merck/Schering-Plough Pharmaceuticals

Merck/Schering-Plough Pharmaceuticals is a joint venture between Merck & Co., Inc. and Schering-Plough Corporation formed to develop and market in the United States new

prescription medicines in cholesterol management. The collaboration includes worldwide markets (excluding Japan). VYTORIN is also marketed as INEGY outside the U.S.

Merck Forward-looking Statement

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements are based on management's current expectations and involve risks and uncertainties, which may cause results to differ materially from those set forth in the statements. The forward-looking statements may include statements regarding product development, product potential or financial performance. No forward-looking statement can be guaranteed and actual results may differ materially from those projected. Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Merck's business, particularly those mentioned in the risk factors and cautionary statements in Item 1A of Merck's Form 10-K for the year ended Dec. 31, 2007, and in any risk factors or cautionary statements contained in the Company's periodic reports on Form 10-Q or current reports on Form 8-K, which the Company incorporates by reference.

Schering-Plough Disclosure Notice

The information in this press release includes certain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements relating to marketing for VYTORIN and ZETIA[®] (ezetimibe). Forward-looking statements relate to expectations or forecasts of future events. Schering-Plough does not assume the obligation to update any forward-looking statement. Many factors could cause actual results to differ materially from Schering-Plough's forward-looking statements, including market forces, economic factors, product availability, patent and other intellectual property protection, current and future branded, generic or over-the-counter competition, the regulatory process, and any developments following regulatory approval, among other uncertainties. For further details about these and other factors that may impact the forward-looking statements, see Schering-Plough's Securities and Exchange Commission filings, including Part I, Item IA. "Risk Factors" in Schering-Plough's 2007 10-K/A.

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Prescribing information and patient product information for VYTORIN is attached.

ZETIA[®] is a registered trademark of MSP Singapore Company, LLC.

ⁱ N Engl J Med 2008; 358:1431-43.

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