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Product News



Merck/Schering-Plough Pharmaceuticals Provides Results of the ENHANCE Trial

Whitehouse Station, N.J., Kenilworth, N.J., Jan. 14, 2008 - Merck/Schering-Plough Pharmaceuticals announced today the primary endpoint and other results of the ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) trial. Merck/Schering-Plough has submitted an abstract on the ENHANCE trial for presentation at the American College of Cardiology meeting, which will be held in March 2008, and is awaiting notification of acceptance from the College.

ENHANCE was a surrogate endpoint trial conducted in 720 patients with Heterozygous Familial Hypercholesterolemia (HeFH), a rare condition that affects approximately 0.2 percent of the population. All analyses were conducted in accordance with the original statistical analysis plan. The primary endpoint was the mean change in the intima-media thickness (IMT) measured at three sites in the carotid arteries (the right and left common carotid, internal carotid and carotid bulb) between patients treated with ezetimibe/simvastatin 10/80 mg versus patients treated with simvastatin 80 mg alone over a two year period.

There was no statistically significant difference between treatment groups on the primary endpoint. The change from baseline in the mean carotid IMT was 0.0111 mm for the ezetimibe/simvastatin 10/80 mg group versus 0.0058 mm for the simvastatin 80 mg group ($p=0.29$). At baseline, the mean carotid IMT measurement for ezetimibe/simvastatin was 0.68 mm and for simvastatin 80 mg was 0.69 mm. There was also no statistically significant difference between the treatment groups for each of the components of the primary endpoint, including the common carotid artery. Key secondary imaging endpoints showed no statistical difference between treatment groups.

The overall incidence rates of treatment-related adverse events, serious adverse events or adverse events leading to discontinuation were generally similar between treatment groups. The incidence of consecutive elevations of serum transaminases ($\geq 3x$ ULN) was 10 out of 356 for ezetimibe/simvastatin (2.8 percent) as compared to 8 out of 360 for simvastatin (2.2 percent). Incidence of elevated creatine phosphokinase ($\geq 10x$ ULN) was 4 out of 356 (1.1 percent) in the ezetimibe/simvastatin group and 8 out of 360 (2.2 percent) in the simvastatin group and two cases (0.6 percent) of $CPK \geq 10x$ ULN associated with muscle symptoms in the ezetimibe/simvastatin group and one case (0.3 percent) in the simvastatin group. There were no cases of rhabdomyolysis. Both medicines were generally well tolerated.

Overall, the safety profiles of ezetimibe/simvastatin and simvastatin alone were similar and generally consistent with their product labels.

After washout, patients enrolled in the study had baseline LDL cholesterol levels of 319 mg/dL in the group randomized to ezetimibe/simvastatin and 318 mg/dL in the simvastatin group. Approximately eighty percent of the patients enrolled in the ENHANCE trial had previously been treated with statins.

In the trial, there was a significant difference in low-density lipoprotein (LDL) cholesterol lowering seen between the treatment groups -- 58 percent LDL cholesterol lowering at 24 months on ezetimibe/simvastatin 10/80 mg as compared to 41 percent at 24 months on simvastatin 80mg alone, ($p<0.01$).

The incidence rates of cardiovascular clinical events in ENHANCE for the ezetimibe/simvastatin and simvastatin groups, respectively, were as follows: cardiovascular death 2 out of 357 vs. 1 out of 363, non-fatal myocardial infarction 3 out of 357 vs. 2 out of 363, non-fatal stroke 1 out of 357 vs. 1 out of 363 and revascularization 6 out of 357 vs. 5 out of 363. There were no non-cardiovascular deaths or incidents of resuscitated cardiac arrests in the ENHANCE trial. This surrogate endpoint study was not powered nor designed to assess cardiovascular clinical event outcomes.

Merck/Schering-Plough Pharmaceuticals is currently conducting three large outcomes trials with ezetimibe/simvastatin, which involve more than 20,000 high-risk patients, including the more than 10,000 patient IMPROVE-IT trial. No incremental benefit of ezetimibe/simvastatin on cardiovascular morbidity and mortality over

and above that demonstrated for simvastatin has been established.

About The ENHANCE Trial

ENHANCE was a multinational, randomized, double-blind, active comparator trial that used digitized single-frame ultrasound technology for imaging purposes. There were 357 HeFH patients randomized to ezetimibe/simvastatin and 363 HeFH patients to simvastatin. The study collected more than 30,000 carotid artery and 10,000 femoral artery images from these patients. HeFH is characterized by markedly elevated plasma concentrations of LDL cholesterol; typically well above the 95th percentile for age and sex.¹

Single-frame ultrasound images were analyzed from the right and left carotid arteries at three sites (the common carotid, the internal carotid and the carotid bulb) and at numerous time points (baseline, 6, 12, 18 and 24 months). Images from the right and left common femoral arteries were analyzed at these same time points as well.

Important information about VYTORIN® (ezetimibe/simvastatin)

VYTORIN contains simvastatin and ezetimibe. VYTORIN is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL cholesterol, Apo B², triglycerides and non-HDL cholesterol and to increase HDL cholesterol in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia.

VYTORIN 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.

VYTORIN is a prescription medicine and should not be taken by people who are hypersensitive to any of its components. VYTORIN 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 VYTORIN.

Selected cautionary information for VYTORIN

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

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 VYTORIN and 2.6 percent for patients treated with VYTORIN 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 VYTORIN 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 VYTORIN when clinically indicated to check for liver problems. People taking VYTORIN 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 (an ingredient in VYTORIN) in patients with moderate or severe hepatic insufficiency, VYTORIN is not recommended in these patients. The safety and effectiveness of VYTORIN with fibrates have not been established; therefore, co-administration with fibrates is not recommended. Caution should be exercised when initiating VYTORIN in patients treated with cyclosporine and in patients with severe renal insufficiency.

VYTORIN 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, 2006, and in its periodic reports on Form 10-Q and 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 potential market 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, 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 II, Item 1A. "Risk Factors" in the Schering-Plough's third quarter 2007 10-Q.

ZETIA and VYTORIN are registered trademarks of MSP Singapore Company LLC.

¹Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science 1986;232:34-47.

²Apo B is the protein compound of lipoproteins, LDL and VLDL, which carry cholesterol in the blood

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