

# **EZETROL combination more effective than LIPITOR or ZOCOR**

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New Studies Show Ezetimibe with Simvastatin Provides

Significantly Greater Reductions in LDL Cholesterol

Compared to LIPITOR® and ZOCOR® Across the Dosing Ranges

Ezetimibe with Simvastatin Provides LDL Cholesterol Reductions

Ranging from 46 to 61 Percent

NEW ORLEANS, La., U.S.A, March 8, 2004 -- Results from three Phase III clinical trials have shown that patients taking ezetimibe (EZETROL®) with simvastatin (ZOCOR®) experience significantly greater reductions in LDL ("bad") cholesterol (LDL-C) compared to reductions seen in patients taking the two most widely prescribed statins, atorvastatin (LIPITOR) or simvastatin alone. The findings of these studies demonstrate that treatment through dual inhibition of two sources of cholesterol provides superior LDL-C efficacy. The studies were presented today at the 53rd Annual Scientific Meeting of the

American College of Cardiology.

EZETROL (ezetimibe) with simvastatin provided greater LDL-C reductions compared to atorvastatin

The first study showed significantly greater LDL-C reduction in patients taking ezetimibe with simvastatin compared to patients taking atorvastatin alone, across the doses tested. The 24-week, 788 patient study examined the effect of ezetimibe (10 mg) taken with doses of simvastatin (ranging from 10 mg to 80 mg) as a fixed single tablet and atorvastatin, ranging from 10 mg to 80 mg. The primary endpoint of this study was the efficacy comparison after the first six-week treatment period. After six weeks of therapy, patients taking ezetimibe 10 mg with simvastatin 10 mg and patients taking ezetimibe 10 mg with simvastatin 20 mg experienced greater LDL-C reductions of 46 percent and 50 percent respectively compared to atorvastatin 10 mg, which produced a 37 percent reduction ( $p < 0.001$  for each versus atorvastatin). “Results from these studies showed that ezetimibe with simvastatin provided greater reductions in LDL cholesterol compared to atorvastatin or simvastatin alone. These results suggest that, if approved, this investigational medicine would offer physicians a different treatment option which targets two sources of cholesterol through dual inhibition of both cholesterol production and absorption,” said Christie Ballantyne, M.D., FACC, FACP, director of the Center for Cardiovascular Disease Prevention and professor of medicine at Baylor College of Medicine/The Methodist DeBakey Heart Center in Houston. EZETROL (ezetimibe) with simvastatin provided greater LDL-C reductions compared to simvastatin (ZOCOR) alone.

A second study compared the LDL-C reduction in patients taking ezetimibe with simvastatin single tablet and simvastatin alone. In this study, patients taking ezetimibe with simvastatin experienced LDL-C reductions of 46 to 61 percent across the doses tested. Ezetimibe 10 mg with simvastatin 20 mg achieved a 51 percent LDL-C reduction compared to reductions of 35 percent and 42 percent, respectively, for simvastatin 20 mg and 40 mg (typical starting doses for simvastatin) alone. This multi-center, double-blind, randomised, placebo-controlled trial was conducted over 12 weeks. After a four-week placebo/diet run-in, 887 patients with LDL-C 145-250 mg/dL and TG  $\leq$  350 mg/dL were randomized to one of ten daily treatments: placebo (n=93); ezetimibe 10 mg (n=92); simvastatin 10, 20, 40, or 80 mg (n=349); ezetimibe 10 mg with simvastatin 10, 20, 40, or 80 mg (n=353).

EZETROL (ezetimibe) with simvastatin provided greater reductions in remnant lipoproteins compared to simvastatin (ZOCOR)

A similar 12-week study compared the effects of the single tablet ezetimibe/simvastatin versus

simvastatin (ZOCOR) across the dosing ranges. After a four-week diet/placebo run-in period, 1,528 patients with LDL-C 145-250 mg/dL and TG <math>\leq 350</math> mg/dL were randomised to one of ten treatment groups: placebo (n=141), ezetimibe 10 mg (n=144), simvastatin 10, 20, 40, or 80 mg (n=597), and ezetimibe/simvastatin 10/10, 10/20, 10/40, and 10/80 mg (n=570). The objective of this analysis was to examine the effects of ezetimibe/simvastatin (single tablet) on remnant-like particle cholesterol (RLP-C), which have been shown to be predictors of future coronary events. RLP-C is a simple assay method for the estimation of triglyceride-rich lipoprotein remnants. An analysis of pooled results across the dosing ranges showed that ezetimibe/simvastatin (single tablet) reduced RLP-C by 41 percent compared to 29 percent for simvastatin.

In addition, study results showed that ezetimibe/simvastatin (single tablet) provided significantly greater LDL-C reductions compared to simvastatin alone (53 percent versus 39 percent, respectively), the study's primary endpoint ( $p < 0.001$ ). These results were similar to the LDL-C reductions seen in patients taking ezetimibe with simvastatin in the other studies presented at ACC. "Levels of remnant lipoproteins may be independent predictors of future coronary events in patients with coronary artery disease," said Harold Bays, M.D., FACP, medical director/president of the Louisville Metabolic and Atherosclerosis Research Center Inc. "Reductions in plasma levels of potentially atherogenic remnant lipoproteins in this study are consistent with the significantly greater LDL-C reductions seen in patients taking ezetimibe/simvastatin compared to those treated with simvastatin alone."

Ezetimibe/simvastatin is currently under review by the Food and Drug Administration and undergoing the Mutual Recognition Procedure in Europe. If approved, ezetimibe/simvastatin (single tablet), along with diet and exercise, would be the first product to reduce cholesterol through dual inhibition by targeting both cholesterol production in the liver and cholesterol absorption in the intestine in one single tablet.

#### About EZETROL

EZETROL (ezetimibe), a cholesterol absorption inhibitor, has been developed and is being marketed by Merck & Co., Inc. (NYSE:MRK) and Schering-Plough Corporation (NYSE:SGP) in connection with a partnership formed by both companies to develop and market worldwide (excluding Japan) new prescription medicines in cholesterol management. Ezetimibe was approved for marketing by the United States Food and Drug Administration on 25 October 2002, and is marketed in the United States as ZETIA™. Following the successful completion of the European Union Mutual Recognition Procedure, EZETROL has now been launched in six European countries -- Germany, the United Kingdom, Switzerland, Sweden, Ireland, and Holland.

## Important information about simvastatin

Simvastatin is marketed by Merck & Co., Inc. under the trade name ZOCOR and is in the class of cholesterol lowering agents known as statins. ZOCOR is used along with diet to improve cholesterol levels in people with high-cholesterol, when diet alone is not enough. ZOCOR has been proven to significantly improve LDL and HDL cholesterol levels, as well as triglyceride levels.

## About Merck

Merck & Co., Inc., which operates in many countries as Merck Sharp & Dohme, is a global research-driven pharmaceutical products and services company. Merck discovers, develops, manufactures and markets a broad range of innovative products to improve human and animal health, directly or through its joint ventures.

## About Schering-Plough

Schering-Plough Corporation is a research-based company engaged in the discovery, development, manufacturing and marketing of pharmaceutical products worldwide.

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