

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

WHITEHOUSE STATION, N.J. & KENILWORTH, N.J.--(BUSINESS WIRE)--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 (greater than or equal to 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 (greater than or equal to 10xULN) 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 greater than or equal to 10xULN 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(R) (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 B(2), 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 (greater than or equal to 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 (greater than or equal to 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(R) (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.

Full prescribing information and patient product information for VYTORIN(R) and ZETIA(R) is attached.

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

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

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

VYTORIN (R) 10/10

(EZETIMIBE 10 MG/SIMVASTATIN 10 MG TABLETS)

VYTORIN (R) 10/20

(EZETIMIBE 10 MG/SIMVASTATIN 20 MG TABLETS)

VYTORIN (R) 10/40

(EZETIMIBE 10 MG/SIMVASTATIN 40 MG TABLETS)

VYTORIN (R) 10/80

(EZETIMIBE 10 MG/SIMVASTATIN 80 MG TABLETS)

DESCRIPTION

VYTORIN contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor.

The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-(3-(4-fluorophenyl)-3(S)-hydroxypropyl)-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is C₂₄H₂₁F₂N₃ and its molecular weight is 409.4.

Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Its structural formula is:

(Graphic Omitted)

Simvastatin, an inactive lactone, is hydrolyzed to the corresponding beta-hydroxyacid form, which is an inhibitor of HMG-CoA reductase. Simvastatin is butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-(2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl)-1-naphthalenyl ester, (1S-(1alpha,3alpha,7beta,8beta(2S*,4S*,-8beta))). The empirical formula of simvastatin is C₂₅H₃₈O₅ and its molecular weight is 418.57.

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol. Its structural formula is:

(Graphic Omitted)

VYTORIN is available for oral use as tablets containing 10 mg of ezetimibe, and 10 mg of simvastatin (VYTORIN 10/10), 20 mg of simvastatin (VYTORIN 10/20), 40 mg of simvastatin (VYTORIN 10/40), or 80 mg of simvastatin (VYTORIN 10/80). Each tablet contains the following inactive ingredients: butylated hydroxyanisole NF, citric acid monohydrate USP, croscarmellose sodium NF, hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, and propyl gallate NF.

CLINICAL PHARMACOLOGY

Background

Clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B), the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of high-density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Mode of Action

VYTORIN

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. VYTORIN contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. VYTORIN reduces elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C through dual inhibition of cholesterol absorption and synthesis.

Ezetimibe

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. In a 2-week clinical study in 18 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo. Ezetimibe had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E and did not impair adrenocortical steroid hormone production.

Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of HMG-CoA reductase inhibitors (see CLINICAL STUDIES).

Simvastatin

Simvastatin reduces cholesterol by inhibiting the conversion of HMG-CoA to mevalonate, an early step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces VLDL and TG and increases HDL-C.

Pharmacokinetics

Absorption

VYTORIN

VYTORIN is bioequivalent to coadministered ezetimibe and simvastatin.

Ezetimibe

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide).

Effect of Food on Oral Absorption

Ezetimibe

Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as 10-mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high-fat meals.

Simvastatin

Relative to the fasting state, the plasma profiles of both active and total inhibitors of HMG-CoA reductase were not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

Distribution

Ezetimibe

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Simvastatin

Both simvastatin and its beta-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. When radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.

Metabolism and Excretion

Ezetimibe

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Minimal oxidative metabolism has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Following oral administration of ¹⁴C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Simvastatin

Simvastatin is a lactone that is readily hydrolyzed in vivo to the corresponding beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is

a basis for an assay in pharmacokinetic studies of the beta-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin. The major active metabolites of simvastatin present in human plasma are the beta-hydroxyacid of simvastatin and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives.

Following an oral dose of 14C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. Plasma concentrations of total radioactivity (simvastatin plus 14C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Since simvastatin undergoes extensive first-pass extraction in the liver, the availability of the drug to the general circulation is low (<5%).

Special Populations

Geriatric Patients

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (\geq 65 years) healthy subjects compared to younger subjects.

Simvastatin

In a study including 16 elderly patients between 70 and 78 years of age who received simvastatin 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age.

Pediatric Patients

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 7 days, the absorption and metabolism of ezetimibe were similar in adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Gender

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

Race

Ezetimibe

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Black and Caucasian subjects. Studies in Asian subjects indicated that the pharmacokinetics of ezetimibe were similar to those seen in Caucasian subjects.

Hepatic Insufficiency

Ezetimibe

After a single 10-mg dose of ezetimibe, the mean exposure (based on area under the curve (AUC)) to total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe increased approximately 3- to 4-fold and 5- to 6-fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency, the mean AUC for total ezetimibe and ezetimibe increased approximately 4-fold compared to healthy subjects.

Renal Insufficiency

Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl (\leq)30 mL/min/1.73 m²), the mean AUC for total ezetimibe and ezetimibe increased approximately 1.5-fold, compared to healthy subjects (n=9).

Simvastatin

Pharmacokinetic studies with another statin having a similar principal route of elimination to that of simvastatin have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal insufficiency (as measured by creatinine clearance).

Drug Interactions (See also PRECAUTIONS, Drug Interactions)

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with simvastatin. Specific pharmacokinetic drug interaction studies with VYTORIN have not been performed.

Cytochrome P450: Ezetimibe had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a "cocktail" study of twelve healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

In a study of 12 healthy volunteers, simvastatin at the 80-mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (CYP3A4) substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and, therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4.

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4.

Simvastatin is a substrate for CYP3A4. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy. (See WARNINGS, Myopathy/Rhabdomyolysis and PRECAUTIONS, Drug Interactions.)

Antacids: In a study of twelve healthy adults, a single dose of antacid (Supralox(TM) 20 mL) administration had no significant effect on the oral bioavailability of total ezetimibe, ezetimibe-glucuronide, or ezetimibe based on AUC values. The C_{max} value of total ezetimibe was decreased by 30%.

Cholestyramine: In a study of forty healthy hypercholesterolemic (LDL-C (\geq)130 mg/dL) adult subjects, concomitant cholestyramine (4 g twice daily) administration decreased the mean AUC of total ezetimibe and ezetimibe approximately 55% and 80%, respectively.

Cyclosporine: In a study of eight post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of $>$ 50 mL/min), stable doses of cyclosporine (75 to 150 mg twice daily) increased the mean AUC and C_{max} values of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively, compared to a historical healthy control population (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m²) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of cyclosporine alone (see PRECAUTIONS, Drug Interactions).

Fenofibrate: In a study of thirty-two healthy hypercholesterolemic (LDL-C (\geq)130 mg/dL) adult subjects, concomitant fenofibrate (200 mg once daily) administration increased the mean C_{max} and AUC values of total ezetimibe approximately 64% and 48%, respectively. Pharmacokinetics of fenofibrate were not significantly affected by ezetimibe (10 mg once daily).

Coadministration of fenofibrate (160 mg daily) with simvastatin (80 mg daily) for 7 days had no effect on plasma AUC (and C_{max}) of either total HMG-CoA reductase inhibitory activity or fenofibric acid; there was a modest reduction (approximately 35%) of simvastatin acid which was not considered clinically significant (see WARNINGS, Myopathy/Rhabdomyolysis, PRECAUTIONS, Drug Interactions).

Gemfibrozil: In a study of twelve healthy adult males, concomitant administration of gemfibrozil (600 mg twice daily) significantly increased the oral bioavailability of total ezetimibe by a factor of 1.7. Ezetimibe (10 mg once daily) did not significantly affect the bioavailability of gemfibrozil.

Coadministration of gemfibrozil (600 mg twice daily for 3 days) with simvastatin (40 mg daily) resulted in clinically significant increases in simvastatin acid AUC (185%) and C_{max} (112%), possibly due to inhibition of simvastatin acid glucuronidation by gemfibrozil (see WARNINGS, Myopathy/Rhabdomyolysis, PRECAUTIONS, Drug Interactions, DOSAGE AND ADMINISTRATION).

Grapefruit Juice: Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study(1), 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with, and 30 and 90 minutes following, a single dose of 60 mg simvastatin on the third day. This regimen of grapefruit juice resulted in mean increases in the concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity (measured using a radioenzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis) of 2.4-fold and 3.6-fold, respectively, and of simvastatin and its beta-hydroxyacid metabolite (measured using a chemical assay -- liquid chromatography/tandem mass spectrometry) of 16-fold and 7-fold, respectively. In a second study, 16 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 20 mg simvastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity (using a validated enzyme inhibition assay different from that used in the first(1) study, both before (for active inhibitors) and after (for total inhibitors) base hydrolysis) of 1.13-fold and 1.18-fold, respectively, and of simvastatin and its beta-hydroxyacid metabolite (measured using a chemical assay -- liquid chromatography/tandem mass spectrometry) of 1.88-fold and 1.31-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.

ANIMAL PHARMACOLOGY

Ezetimibe

The hypocholesterolemic effect of ezetimibe was evaluated in cholesterol-fed Rhesus monkeys, dogs, rats, and mouse models of human cholesterol metabolism. Ezetimibe was found to have an ED₅₀ value of 0.5 ug/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED₅₀ values in dogs, rats, and mice were 7, 30, and 700 ug/kg/day, respectively. These results are consistent with ezetimibe being a potent cholesterol absorption inhibitor.

In a rat model, where the glucuronide metabolite of ezetimibe (ezetimibe-glucuronide) was administered intraduodenally, the metabolite was as potent as ezetimibe in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug.

In 1-month studies in dogs given ezetimibe (0.03 to 300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14-day study in mice given ezetimibe (0.3 to 5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

A series of acute preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of 14C-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethyl estradiol, or the fat-soluble vitamins A and D.

In 4- to 12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with HMG-CoA reductase inhibitors (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

CLINICAL STUDIES

Primary Hypercholesterolemia

VYTORIN

VYTORIN reduces total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C in patients with hypercholesterolemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy.

VYTORIN is effective in men and women with hypercholesterolemia. Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of VYTORIN.

Five multicenter, double-blind studies conducted with either VYTORIN or coadministered ezetimibe and simvastatin equivalent to VYTORIN in patients with primary hypercholesterolemia are reported: two were comparisons with simvastatin, two were comparisons with atorvastatin, and one was a comparison with rosuvastatin.

In a multicenter, double-blind, placebo-controlled, 12-week trial, 1528 hypercholesterolemic patients were randomized to one of ten treatment groups: placebo, ezetimibe (10 mg), simvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or VYTORIN (10/10, 10/20, 10/40, or 10/80).

When patients receiving VYTORIN were compared to those receiving all doses of simvastatin, VYTORIN significantly lowered total-C, LDL-C, Apo B, TG, and non-HDL-C. The effects of VYTORIN on HDL-C were similar to the effects seen with simvastatin. Further analysis showed VYTORIN significantly increased HDL-C compared with placebo. (See Table 1.) The lipid response to VYTORIN was similar in patients with TG levels greater than or less than 200 mg/dL.

Table 1
Response to VYTORIN in Patients with Primary Hypercholesterolemia
(Meana % Change from Untreated Baselineb)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TGa	Non- HDL-C
Pooled data (All VYTORIN doses)c	609	-38	-53	-42	+7	-24	-49
Pooled data (All simvastatin doses)c	622	-28	-39	-32	+7	-21	-36
Ezetimibe 10 mg	149	-13	-19	-15	+5	-11	-18
Placebo	148	-1	-2	0	0	-2	-2
VYTORIN by dose							
10/10	152	-31	-45	-35	+8	-23	-41
10/20	156	-36	-52	-41	+10	-24	-47
10/40	147	-39	-55	-44	+6	-23	-51
10/80	154	-43	-60	-49	+6	-31	-56
Simvastatin by dose							
10 mg	158	-23	-33	-26	+5	-17	-30
20 mg	150	-24	-34	-28	+7	-18	-32
40 mg	156	-29	-41	-33	+8	-21	-38
80 mg	158	-35	-49	-39	+7	-27	-45

a For triglycerides, median % change from baseline

b Baseline - on no lipid-lowering drug

c VYTORIN doses pooled (10/10-10/80) significantly reduced total-C, LDL-C, Apo B, TG, and non-HDL-C compared to simvastatin, and significantly increased HDL-C compared to placebo.

In a multicenter, double-blind, controlled, 23-week study, 710 patients with known CHD or CHD risk equivalents, as defined by the NCEP ATP III guidelines, and an LDL-C (\geq) 130 mg/dL were randomized to one of four treatment groups: coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/10, 10/20, and 10/40), or simvastatin 20 mg. Patients not reaching an LDL-C <100 mg/dL had their simvastatin dose titrated at 6-week

intervals to a maximal dose of 80 mg.

At Week 5, the LDL-C reductions with VYTORIN 10/10, 10/20, or 10/40 were significantly larger than with simvastatin 20 mg (see Table 2).

Table 2
Response to VYTORIN after 5 Weeks in Patients with CHD or CHD Risk
Equivalents and an LDL-C (\geq)130 mg/dL

	Simvastatin	VYTORIN	VYTORIN	VYTORIN
	20 mg	10/10	10/20	10/40
N	253	251	109	97
Mean baseline LDL-C	174	165	167	171
Percent change LDL-C	-38	-47	-53	-59

In a multicenter, double-blind, 6-week study, 1902 patients with primary hypercholesterolemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to one of eight treatment groups: VYTORIN (10/10, 10/20, 10/40, or 10/80) or atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg).

Across the dosage range, when patients receiving VYTORIN were compared to those receiving milligram-equivalent statin doses of atorvastatin, VYTORIN lowered total-C, LDL-C, Apo B, and non-HDL-C significantly more than atorvastatin. Only the 10/40 mg and 10/80 mg VYTORIN doses increased HDL-C significantly more than the corresponding milligram-equivalent statin dose of atorvastatin. The effects of VYTORIN on TG were similar to the effects seen with atorvastatin. (See Table 3.)

Table 3
Response to VYTORIN and Atorvastatin in Patients with Primary
Hypercholesterolemia
(Meana % Change from Untreated Baselineb)

Treatment (Daily Dose)	N	Total- C _c	LDL- C _c	Apo B _c	HDL- C _c	TG _a	Non- HDL- C _c
VYTORIN by dose							
10/10	230	-34d	-47d	-37d	+8	-26	-43d
10/20	233	-37d	-51d	-40d	+7	-25	-46d
10/40	236	-41d	-57d	-46d	+9d	-27	-52d
10/80	224	-43d	-59d	-48d	+8d	-31	-54d
Atorvastatin by dose							
10 mg	235	-27	-36	-31	+7	-21	-34
20 mg	230	-32	-44	-37	+5	-25	-41
40 mg	232	-36	-48	-40	+4	-24	-45
80 mg	230	-40	-53	-44	+1	-32	-50

- a For triglycerides, median % change from baseline
- b Baseline - on no lipid-lowering drug
- c VYTORIN doses pooled (10/10-10/80) provided significantly greater reductions in total-C, LDL-C, Apo B, and non-HDL-C compared to atorvastatin doses pooled (10-80).
- d $p < 0.05$ for difference with atorvastatin at equal mg doses of the simvastatin component

In a multicenter, double-blind, 24-week, forced titration study, 788 patients with primary hypercholesterolemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to receive coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/10 and 10/20) or atorvastatin 10 mg. For all three treatment groups, the dose of the statin was titrated at 6-week intervals to 80 mg. At each pre-specified dose comparison,

VYTORIN lowered LDL-C to a greater degree than atorvastatin (see Table 4).

Table 4
Response to VYTORIN and Atorvastatin in Patients with Primary
Hypercholesterolemia
(Meana % Change from Untreated Baselineb)

Treatment	N	Total- C	LDL- C	Apo B	HDL- C	TGa	Non-
							HDL- C

Week 6							

Atorvastatin 10 mgc	262	-28	-37	-32	+5	-23	-35

VYTORIN 10/10d	263	-34f	-46f	-38f	+8f	-26	-43f

VYTORIN 10/20e	263	-36f	-50f	-41f	+10f	-25	-46f

Week 12							

Atorvastatin 20 mg	246	-33	-44	-38	+7	-28	-42

VYTORIN 10/20	250	-37f	-50f	-41f	+9	-28	-46f

VYTORIN 10/40	252	-39f	-54f	-45f	+12f	-31	-50f

Week 18							

Atorvastatin 40 mg	237	-37	-49	-42	+8	-31	-47

VYTORIN 10/40g	482	-40f	-56f	-45f	+11f	-32	-52f

Week 24							

Atorvastatin 80 mg	228	-40	-53	-45	+6	-35	-50

VYTORIN 10/80g	459	-43f	-59f	-49f	+12f	-35	-55f

- a For triglycerides, median % change from baseline
- b Baseline - on no lipid-lowering drug
- c Atorvastatin: 10 mg start dose titrated to 20 mg, 40 mg, and 80 mg through Weeks 6, 12, 18, and 24
- d VYTORIN: 10/10 start dose titrated to 10/20, 10/40, and 10/80 through Weeks 6, 12, 18, and 24
- e VYTORIN: 10/20 start dose titrated to 10/40, 10/40, and 10/80 through Weeks 6, 12, 18, and 24
- f $p(<=)0.05$ for difference with atorvastatin in the specified week
- g Data pooled for common doses of VYTORIN at Weeks 18 and 24.

In a multicenter, double-blind, 6-week study, 2959 patients with primary hypercholesterolemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to one of six treatment groups: VYTORIN (10/20, 10/40, or 10/80) or rosuvastatin (10 mg, 20 mg, or 40 mg).

The effects of VYTORIN and rosuvastatin on total-C, LDL-C, Apo B, TG, non-HDL-C and HDL-C are shown in Table 5.

Table 5
Response to VYTORIN and Rosuvastatin in Patients with Primary
Hypercholesterolemia
(Meana % Change from Untreated Baselineb)

Treatment (Daily Dose)	N	Total- Cc	LDL- Cc	Apo Bc	HDL- C	TGa	Non-
							HDL- Cc

VYTORIN by dose							

10/20	476	-37d	-52d	-42d	+7	-23d	-47d

10/40	477	-39e	-55e	-44e	+8	-27	-50e

10/80	474	-44f	-61f	-50f	+8	-30f	-56f

Rosuvastatin by dose							
10 mg	475	-32	-46	-37	+7	-20	-42
20 mg	478	-37	-52	-43	+8	-26	-48
40 mg	475	-41	-57	-47	+8	-28	-52

a For triglycerides, median % change from baseline

b Baseline - on no lipid-lowering drug

c VYTORIN doses pooled (10/20-10/80) provided significantly greater reductions in total-C, LDL-C, Apo B, and non-HDL-C compared to rosuvastatin doses pooled (10-40 mg).

d $p < 0.05$ vs. rosuvastatin 10 mg

e $p < 0.05$ vs. rosuvastatin 20 mg

f $p < 0.05$ vs. rosuvastatin 40 mg

In a multicenter, double-blind, 24-week trial, 214 patients with type 2 diabetes mellitus treated with thiazolidinediones (rosiglitazone or pioglitazone) for a minimum of 3 months and simvastatin 20 mg for a minimum of 6 weeks, were randomized to receive either simvastatin 40 mg or the coadministered active ingredients equivalent to VYTORIN 10/20. The median LDL-C and HbA1c levels at baseline were 89 mg/dL and 7.1%, respectively.

VYTORIN 10/20 was significantly more effective than doubling the dose of simvastatin to 40 mg. The median percent changes from baseline for VYTORIN vs simvastatin were: LDL-C -25% and -5%; total-C -16% and -5%; Apo B -19% and -5%; and non-HDL-C -23% and -5%. Results for HDL-C and TG between the two treatment groups were not significantly different.

Ezetimibe

In two multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, ezetimibe significantly lowered total-C (-13%), LDL-C (-19%), Apo B (-14%), and TG (-8%), and increased HDL-C (+3%) compared to placebo. Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

Simvastatin

In two large, placebo-controlled clinical trials, the Scandinavian Simvastatin Survival Study (N=4,444 patients) and the Heart Protection Study (N=20,536 patients), the effects of treatment with simvastatin were assessed in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease. Simvastatin was proven to reduce: the risk of total mortality by reducing CHD deaths; the risk of non-fatal myocardial infarction and stroke; and the need for coronary and non-coronary revascularization procedures.

No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

Homozygous Familial Hypercholesterolemia (HoFH)

A double-blind, randomized, 12-week study was performed in patients with a clinical and/or genotypic diagnosis of HoFH. Data were analyzed from a subgroup of patients (n=14) receiving simvastatin 40 mg at baseline. Increasing the dose of simvastatin from 40 to 80 mg (n=5) produced a reduction of LDL-C of 13% from baseline on simvastatin 40 mg. Coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/40 and 10/80 pooled, n=9), produced a reduction of LDL-C of 23% from baseline on simvastatin 40 mg. In those patients coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/80, n=5), a reduction of LDL-C of 29% from baseline on simvastatin 40 mg was produced.

INDICATIONS AND USAGE

Primary Hypercholesterolemia

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

Homozygous Familial Hypercholesterolemia (HoFH)

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

Therapy with lipid-altering agents should be a component of multiple risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to an appropriate diet (including restriction of saturated fat and cholesterol) and when the response to diet and other non-pharmacological measures has been inadequate. (See NCEP Adult Treatment Panel (ATP) III Guidelines, summarized in Table 6.)

Table 6
Summary of NCEP ATP III Guidelines

Risk Category	LDL Goal (mg/dL)	LDL Level at	
		Which to Initiate Therapeutic Lifestyle Changes ^a (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents ^b (10-year risk >20%) ^c	<100	(≥)100	(≥)130 (100-129: drug optional) ^d
2+ Risk factors ^e (10-year risk (≤)20%) ^c	<130	(≥)130	10-year risk 10- 20%: (≥)130 ^c 10-year risk <10%: (≥)160 ^c
0-1 Risk factor ^f	<160	(≥)160	(≥)190 (160-189: LDL- lowering drug optional)

a Therapeutic lifestyle changes include: 1) dietary changes: reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg per day), and enhancing LDL lowering with plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10-25 g/d), 2) weight reduction, and 3) increased physical activity.

b CHD risk equivalents comprise: diabetes, multiple risk factors that confer a 10-year risk for CHD >20%, and other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm and symptomatic carotid artery disease).

c Risk assessment for determining the 10-year risk for developing CHD is carried out using the Framingham risk scoring. Refer to JAMA, May 16, 2001; 285 (19): 2486-2497, or the NCEP website (<http://www.nhlbi.nih.gov>) for more details.

d Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

e Major risk factors (exclusive of LDL cholesterol) that modify LDL goals include cigarette smoking, hypertension (BP (≥)140/90 mm Hg or on anti-hypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), age (men (≥)45 years; women (≥)55 years). HDL cholesterol (≥)60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

f Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Prior to initiating therapy with VYTORIN, secondary causes for dyslipidemia (i.e., diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C (progestins, anabolic steroids, and corticosteroids)), should be excluded or, if appropriate, treated. A lipid profile should be performed to measure total-C, LDL-C, HDL-C and TG. For TG levels >400 mg/dL (>4.5 mmol/L), LDL-C concentrations should be determined by ultracentrifugation.

At the time of hospitalization for an acute coronary event, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of

LDL-lowering therapy before or at discharge.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations in serum transaminases (see WARNINGS, Liver Enzymes).

Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as simvastatin to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, VYTORIN is contraindicated during pregnancy and in nursing mothers. VYTORIN should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, VYTORIN should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, Pregnancy).

WARNINGS

Myopathy/Rhabdomyolysis

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipid-lowering drugs. In clinical trials, the incidence of CK >10 X the upper limit of normal (ULN) was 0.2% for VYTORIN. (See PRECAUTIONS, Skeletal Muscle.)

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase above 10 X ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,050 patients were treated with simvastatin with 24,747 (approximately 60%) treated for at least 4 years, the incidence of myopathy was approximately 0.02%, 0.08% and 0.53% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

All patients starting therapy with VYTORIN or whose dose of VYTORIN is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. VYTORIN therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when simvastatin treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients taking VYTORIN merit closer monitoring. Therapy with VYTORIN should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Because VYTORIN contains simvastatin, the risk of myopathy/rhabdomyolysis is increased by concomitant use of VYTORIN with the following:

Potent inhibitors of CYP3A4: Simvastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). When simvastatin is used with a potent inhibitor of CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of simvastatin.

The use of VYTORIN concomitantly with the potent CYP3A4 inhibitors itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided. Concomitant use of other medicines labeled as having a potent inhibitory effect on

CYP3A4 should be avoided unless the benefits of combined therapy outweigh the increased risk. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with VYTORIN should be suspended during the course of treatment.

Other drugs:

Gemfibrozil, particularly with higher doses of VYTORIN: There is an increased risk of myopathy when simvastatin is used concomitantly with fibrates (especially gemfibrozil). The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with gemfibrozil. Therefore, although not recommended, if VYTORIN is used in combination with gemfibrozil, the dose should not exceed 10/10 mg daily. (See CLINICAL PHARMACOLOGY, Pharmacokinetics; PRECAUTIONS, Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone, Other drug interactions, and DOSAGE AND ADMINISTRATION.)

Other lipid-lowering drugs (other fibrates or (\geq)1 g/day of niacin): Caution should be used when prescribing other fibrates or lipid-lowering doses (\geq 1 g/day) of niacin with VYTORIN, as these agents can cause myopathy when given alone. The safety and effectiveness of VYTORIN administered with other fibrates or (\geq)1 g/day) of niacin have not been established. Therefore, the benefit of further alterations in lipid levels by the combined use of VYTORIN with other fibrates or niacin should be carefully weighed against the potential risks of these drug combinations. (See CLINICAL PHARMACOLOGY, Pharmacokinetics; PRECAUTIONS, Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone, Other drug interactions, and DOSAGE AND ADMINISTRATION.)

Cyclosporine or danazol with higher doses of VYTORIN: The dose of VYTORIN should not exceed 10/10 mg daily in patients receiving concomitant medication with cyclosporine or danazol. The benefits of the use of VYTORIN in patients receiving cyclosporine or danazol should be carefully weighed against the risks of these combinations. (See CLINICAL PHARMACOLOGY, Pharmacokinetics; PRECAUTIONS, Drug Interactions, Other drug interactions.)

Amiodarone or verapamil with higher doses of VYTORIN: The dose of VYTORIN should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of VYTORIN at doses higher than 10/20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. (See PRECAUTIONS, Drug Interactions, Other drug interactions.) In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone. In an analysis of clinical trials involving 25,248 patients treated with simvastatin 20 to 80 mg, the incidence of myopathy was higher in patients receiving verapamil and simvastatin (4/635; 0.63%) than in patients taking simvastatin without a calcium channel blocker (13/21,224; 0.061%).

Prescribing recommendations for interacting agents are summarized in Table 7 (see also CLINICAL PHARMACOLOGY, Pharmacokinetics; PRECAUTIONS, Drug Interactions; DOSAGE AND ADMINISTRATION).

TABLE 7
Drug Interactions Associated with Increased Risk of
Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone Fibrates*	Avoid VYTORIN
Cyclosporine Danazol	Do not exceed 10/10 mg VYTORIN daily
Amiodarone Verapamil	Do not exceed 10/20 mg VYTORIN daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

*For additional information regarding gemfibrozil, see DOSAGE AND ADMINISTRATION.

Liver Enzymes

In three placebo-controlled, 12-week trials, the incidence of consecutive elevations (\geq 3 X ULN) in serum transaminases was 1.7% overall for patients treated with VYTORIN and appeared to be dose-related with an incidence of 2.6% for patients treated with VYTORIN 10/80. In controlled long-term (48-week) extensions, which included both newly-treated and previously-treated patients, the incidence of consecutive elevations (\geq 3 X ULN) in serum transaminases was 1.8% overall and 3.6% for patients treated with VYTORIN 10/80. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

It is recommended that liver function tests be performed before the initiation of treatment with VYTORIN, and thereafter when clinically indicated. Patients titrated to the 10/80-mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 X ULN or greater persist, withdrawal of therapy with VYTORIN is recommended.

VYTORIN should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of VYTORIN.

PRECAUTIONS

Information for Patients

Patients should be advised about substances they should not take concomitantly with VYTORIN and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see list below and WARNINGS, Myopathy/Rhabdomyolysis). Patients should also be advised to inform other physicians prescribing a new medication that they are taking VYTORIN.

Skeletal Muscle

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported regardless of causality. Most patients who developed rhabdomyolysis were taking a statin prior to initiating ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to agents known to be associated with increased risk of rhabdomyolysis, such as fibrates.

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, VYTORIN is not recommended in these patients. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations.)

Drug Interactions (See also CLINICAL PHARMACOLOGY, Drug Interactions)

VYTORIN

CYP3A4 Interactions

Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of the simvastatin component of VYTORIN.

See WARNINGS, Myopathy/Rhabdomyolysis, and CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions.

Itraconazole

Ketoconazole

Erythromycin

Clarithromycin

Tellithromycin

HIV protease inhibitors

Nefazodone

Large quantities of grapefruit juice (>1 quart daily)

Interactions with lipid-lowering drugs that can cause myopathy when given alone

See WARNINGS, Myopathy/Rhabdomyolysis.

The risk of myopathy is increased by gemfibrozil and to a lesser extent by other fibrates and niacin (nicotinic acid) (≥ 1 g/day).

Other drug interactions

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of VYTORIN (see WARNINGS, Myopathy/Rhabdomyolysis).

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding VYTORIN to cholestyramine may be reduced by this interaction.

Cyclosporine or Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol particularly with higher doses of VYTORIN (see CLINICAL PHARMACOLOGY, Pharmacokinetics and WARNINGS, Myopathy/Rhabdomyolysis).

Caution should be exercised when using VYTORIN and cyclosporine concomitantly due to increased exposure to both ezetimibe and cyclosporine (see DOSAGE AND ADMINISTRATION, Patients taking Cyclosporine or Danazol). Cyclosporine concentrations should be monitored in patients receiving VYTORIN and cyclosporine (see CLINICAL PHARMACOLOGY, Drug Interactions).

The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. In a pharmacokinetic study in post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 mL/min), concomitant cyclosporine administration increased the mean AUC and C_{max} of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively. In a separate study, the total ezetimibe exposure increased 12-fold in one renal transplant patient with severe renal insufficiency receiving multiple medications, including cyclosporine. (See CLINICAL PHARMACOLOGY, Drug Interactions and WARNINGS, Myopathy/Rhabdomyolysis.)

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in plasma digoxin concentrations compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when VYTORIN is initiated.

Fibrates: The safety and effectiveness of VYTORIN administered with fibrates have not been established.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see ANIMAL PHARMACOLOGY). Coadministration of VYTORIN with fibrates is not recommended until use in patients is studied. (See WARNINGS, Myopathy/Rhabdomyolysis.)

Warfarin: Simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in a normal volunteer study and in a hypercholesterolemic patient study, respectively. With other statins, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting VYTORIN and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the

intervals usually recommended for patients on coumarin anticoagulants. If the dose of VYTORIN is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. There have been post-marketing reports of increased International Normalized Ratio (INR) in patients who had ezetimibe added to warfarin. Most of these patients were also on other medications.

The effect of VYTORIN on the prothrombin time has not been studied.

Ezetimibe

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold.

Simvastatin

Propranolol: In healthy male volunteers there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of simvastatin and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

Carcinogenesis, Mutagenesis, Impairment of Fertility

VYTORIN

No animal carcinogenicity or fertility studies have been conducted with the combination of ezetimibe and simvastatin. The combination of ezetimibe with simvastatin did not show evidence of mutagenicity in vitro in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed in vitro in a chromosomal aberration assay in human peripheral blood lymphocytes with ezetimibe and simvastatin with or without metabolic activation. There was no evidence of genotoxicity at doses up to 600 mg/kg with the combination of ezetimibe and simvastatin (1:1) in the in vivo mouse micronucleus test.

Ezetimibe

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on AUC0-24hr for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on AUC0-24hr for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed in vitro in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed in vitro in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the in vivo mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on AUC0-24hr for total ezetimibe).

Simvastatin

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an in vitro alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an in vitro chromosome aberration study in CHO cells, or an in vivo chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m²), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category: X

See CONTRAINDICATIONS.

VYTORIN

As safety in pregnant women has not been established, treatment should be immediately discontinued as soon as pregnancy is recognized. VYTORIN should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Ezetimibe

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple-dose studies of ezetimibe coadministered with HMG-CoA reductase inhibitors (statins) in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in coadministration therapy compared to monotherapy.

Simvastatin

Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 3 times (rat) or 3 times (rabbit) the human exposure based on mg/m² surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review(2) of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Labor and Delivery

The effects of VYTORIN on labor and delivery in pregnant women are unknown.

Nursing Mothers

In rat studies, exposure to ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe or simvastatin are excreted into human breast milk. Because a small amount of another drug in the same class as simvastatin is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women who are nursing should not take VYTORIN (see CONTRAINDICATIONS).

Pediatric Use

VYTORIN

There are insufficient data for the safe and effective use of VYTORIN in pediatric patients. (See Ezetimibe and Simvastatin below.)

Ezetimibe

The pharmacokinetics of ezetimibe in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ezetimibe in the pediatric population is limited to 4 patients (9 to 17 years) with homozygous sitosterolemia and 5 patients (11 to 17 years) with HoFH. Treatment with ezetimibe in children (<10 years) is not recommended.

Simvastatin

Safety and effectiveness of simvastatin in patients 10-17 years of age

Merck & Co., Inc.

with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. Doses greater than 40 mg have not been studied in this population. In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on therapy with simvastatin (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

Geriatric Use

Of the patients who received VYTORIN in clinical studies, 792 were 65 and older (this included 176 who were 75 and older). The safety of VYTORIN was similar between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, Special Populations and ADVERSE REACTIONS.)

ADVERSE REACTIONS

VYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. VYTORIN was generally well tolerated.

Table 8 summarizes the frequency of clinical adverse experiences reported in (\geq)2% of patients treated with VYTORIN (n=1236) and at an incidence greater than placebo regardless of causality assessment from three similarly designed, placebo-controlled trials.

Table 8*
Clinical Adverse Events Occurring in
(\geq)2% of Patients Treated with VYTORIN and at an Incidence Greater
than Placebo, Regardless of Causality

Body System/Organ Class Adverse Event	Placebo	Ezetimibe	Simvastatin**	VYTORIN**
	(%) n=311	10 mg (%) n=302	(%) n=1234	(%) n=1236

Body as a whole - general disorders				
Headache	6.4	6.0	5.9	6.8
Infection and infestations				
Influenza	1.0	1.0	1.9	2.6
Upper respiratory tract infection	2.6	5.0	5.0	3.9
Musculoskeletal and connective tissue disorders				
Myalgia	2.9	2.3	2.6	3.5
Pain in extremity	1.3	3.0	2.0	2.3

*Includes two placebo-controlled combination studies in which the active ingredients equivalent to VYTORIN were coadministered and one placebo-controlled study in which VYTORIN was administered.

**All doses.

Post-marketing Experience

The adverse reactions reported for VYTORIN are consistent with those previously reported with ezetimibe and/or simvastatin.

Ezetimibe

Other adverse experiences reported with ezetimibe in placebo-controlled studies, regardless of causality assessment: Body as a whole - general disorders: fatigue; Gastrointestinal system disorders: abdominal pain, diarrhea; Infection and infestations: infection viral, pharyngitis, sinusitis; Musculoskeletal system disorders: arthralgia, back pain; Respiratory system disorders: coughing.

Post-marketing Experience

The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment:

Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria; arthralgia; myalgia; elevations in liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; dizziness; depression; cholelithiasis; cholecystitis; elevated creatine phosphokinase; and, very rarely, myopathy/rhabdomyolysis (see WARNINGS, Myopathy/Rhabdomyolysis).

Simvastatin

Other adverse experiences reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment: Body as a whole - general disorders: asthenia; Eye disorders: cataract; Gastrointestinal system disorders: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea; Skin and subcutaneous tissue disorders: eczema, pruritus, rash.

The following effects have been reported with other HMG-CoA reductase inhibitors. Not all the effects listed below have necessarily been associated with simvastatin therapy.

Musculoskeletal system disorders: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Nervous system disorders: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances.

Ear and labyrinth disorders: vertigo.

Psychiatric disorders: anxiety, insomnia, depression, loss of libido.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal system disorders: pancreatitis, vomiting.

Hepatobiliary disorders: hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, hepatic failure, and hepatoma.

Metabolism and nutrition disorders: anorexia.

Skin and subcutaneous tissue disorders: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive system and breast disorders: gynecomastia, erectile dysfunction.

Eye disorders: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ -glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS,

Liver Enzymes). About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, Myopathy/Rhabdomyolysis).

Concomitant Lipid-Lowering Therapy

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine.

Adolescent Patients (ages 10-17 years)

In a 48-week controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with simvastatin (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, Pediatric Use).

OVERDOSAGE

VYTORIN

No specific treatment of overdose with VYTORIN can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed.

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, was generally well tolerated.

A few cases of overdose have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

Simvastatin

A few cases of overdose with simvastatin have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

The dialyzability of simvastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving VYTORIN and should continue on this diet during treatment with VYTORIN. The dosage should be individualized according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response. (See NCEP Adult Treatment Panel (ATP) III Guidelines, summarized in Table 6.) VYTORIN should be taken as a single daily dose in the evening, with or without food.

The dosage range is 10/10 mg/day through 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL-C reductions. Patients who require a larger reduction in LDL-C (greater than 55%) may be started at 10/40 mg/day. After initiation or titration of VYTORIN, lipid levels may be analyzed after 2 or more weeks and dosage adjusted, if needed. See below for dosage recommendations for patients receiving certain concomitant therapies and for those with renal insufficiency.

Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage for patients with homozygous familial hypercholesterolemia is VYTORIN 10/40 mg/day or 10/80 mg/day in the evening. VYTORIN should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Patients with Hepatic Insufficiency

No dosage adjustment is necessary in patients with mild hepatic insufficiency (see PRECAUTIONS, Hepatic Insufficiency).

Patients with Renal Insufficiency

No dosage adjustment is necessary in patients with mild or moderate renal insufficiency. However, for patients with severe renal insufficiency, VYTORIN should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 5 mg or higher. Caution should be exercised when VYTORIN is administered to these patients and they should be closely monitored (see CLINICAL PHARMACOLOGY, Pharmacokinetics and WARNINGS, Myopathy/Rhabdomyolysis).

Geriatric Patients

No dosage adjustment is necessary in geriatric patients (see CLINICAL PHARMACOLOGY, Special Populations).

Coadministration with Bile Acid Sequestrants

Dosing of VYTORIN should occur either (\geq)2 hours before or (\geq)4 hours after administration of a bile acid sequestrant (see PRECAUTIONS, Drug Interactions).

Patients taking Cyclosporine or Danazol

Caution should be exercised when initiating VYTORIN in the setting of cyclosporine. In patients taking cyclosporine or danazol, VYTORIN should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 5 mg or higher. The dose of VYTORIN should not exceed 10/10 mg/day.

Patients taking Amiodarone or Verapamil

In patients taking amiodarone or verapamil concomitantly with VYTORIN, the dose should not exceed 10/20 mg/day (see WARNINGS, Myopathy/Rhabdomyolysis and PRECAUTIONS, Drug Interactions, Other drug interactions).

Patients taking other Concomitant Lipid-Lowering Therapy

The safety and effectiveness of VYTORIN administered with fibrates have not been established. Therefore, the combination of VYTORIN and fibrates should be avoided (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions, Other drug interactions).

There is an increased risk of myopathy when simvastatin is used concomitantly with fibrates (especially gemfibrozil). Therefore, although not recommended, if VYTORIN is used in combination with gemfibrozil, the dose should not exceed 10/10 mg daily (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions, Other drug interactions).

HOW SUPPLIED

No. 3873 -- Tablets VYTORIN 10/10 are white to off-white capsule-shaped tablets with code "311" on one side.

They are supplied as follows:

NDC 66582-311-31 bottles of 30

NDC 66582-311-54 bottles of 90

NDC 66582-311-82 bottles of 1000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-311-87 bottles of 10,000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-311-28 unit dose packages of 100.

No. 3874 -- Tablets VYTORIN 10/20 are white to off-white capsule-shaped tablets with code "312" on one side.

They are supplied as follows:

NDC 66582-312-31 bottles of 30

NDC 66582-312-54 bottles of 90

NDC 66582-312-82 bottles of 1000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-312-87 bottles of 10,000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-312-28 unit dose packages of 100.

No. 3875 -- Tablets VYTORIN 10/40 are white to off-white capsule-shaped tablets with code "313" on one side.

They are supplied as follows:

NDC 66582-313-31 bottles of 30

NDC 66582-313-54 bottles of 90

NDC 66582-313-74 bottles of 500 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-313-86 bottles of 5000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-313-52 unit dose packages of 50.

No. 3876 -- Tablets VYTORIN 10/80 are white to off-white capsule-shaped tablets with code "315" on one side.

They are supplied as follows:

NDC 66582-315-31 bottles of 30

NDC 66582-315-54 bottles of 90

NDC 66582-315-74 bottles of 500 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-315-66 bottles of 2500 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-315-52 unit dose packages of 50.

Storage

Store at 20-25degreeC (68-77degreeF). (See USP Controlled Room Temperature.) Keep container tightly closed.

Storage of 10,000, 5000, and 2500 count bottles

Store bottle of 10,000 VYTORIN 10/10 and 10/20, 5000 VYTORIN 10/40, and 2500 VYTORIN 10/80 capsule-shaped tablets at 20-25degreeC (68-77degreeF). (See USP Controlled Room Temperature.) Store in original container until time of use. When product container is subdivided, repackage into a tightly-closed, light-resistant container. Entire contents must be repackaged immediately upon opening.

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VYTORIN(R) (ezetimibe/simvastatin) Tablets

Patient Information about VYTORIN (VI-tor-in)
Generic name: ezetimibe/simvastatin tablets

Read this information carefully before you start taking VYTORIN. Review this information each time you refill your prescription for VYTORIN as there may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about VYTORIN, ask your doctor. Only your doctor can determine if VYTORIN is right for you.

What is VYTORIN?

VYTORIN contains two cholesterol-lowering medications, ezetimibe and simvastatin, available as a tablet in four strengths:

-- VYTORIN 10/10 (ezetimibe 10 mg/simvastatin 10 mg)

-- VYTORIN 10/20 (ezetimibe 10 mg/simvastatin 20 mg)

-- VYTORIN 10/40 (ezetimibe 10 mg/simvastatin 40 mg)

-- VYTORIN 10/80 (ezetimibe 10 mg/simvastatin 80 mg)

VYTORIN is a medicine used to lower levels of total cholesterol, LDL (bad) cholesterol, and fatty substances called triglycerides in the blood. In addition, VYTORIN raises levels of HDL (good) cholesterol. It is used for patients who cannot control their cholesterol levels by diet alone. You should stay on a cholesterol-lowering diet while taking this medicine.

VYTORIN works to reduce your cholesterol in two ways. It reduces the cholesterol absorbed in your digestive tract, as well as the cholesterol your body makes by itself. VYTORIN does not help you lose weight.

For more information about cholesterol, see the section called "What should I know about high cholesterol?"

Who should not take VYTORIN?

Do not take VYTORIN:

- If you are allergic to ezetimibe or simvastatin, the active ingredients in VYTORIN, or to the inactive ingredients. For a list of inactive ingredients, see the "Inactive

ingredients" section at the end of this information sheet.

- If you have active liver disease or repeated blood tests indicating possible liver problems.
- If you are pregnant, or think you may be pregnant, or planning to become pregnant or breast-feeding.

VYTORIN is not recommended for use in children under 10 years of age.

What should I tell my doctor before and while taking VYTORIN?

Tell your doctor right away if you experience unexplained muscle pain, tenderness, or weakness. This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage.

The risk of muscle breakdown is greater at higher doses of VYTORIN.

The risk of muscle breakdown is greater in patients with kidney problems.

Taking VYTORIN with certain substances can increase the risk of muscle problems. It is particularly important to tell your doctor if you are taking any of the following:

- cyclosporine
- danazol
- antifungal agents (such as itraconazole or ketoconazole)
- fibric acid derivatives (such as gemfibrozil, bezafibrate, or fenofibrate)
- the antibiotics erythromycin, clarithromycin, and telithromycin
- HIV protease inhibitors (such as indinavir, nelfinavir, ritonavir, and saquinavir)
- the antidepressant nefazodone
- amiodarone (a drug used to treat an irregular heartbeat)
- verapamil (a drug used to treat high blood pressure, chest pain associated with heart disease, or other heart conditions)
- large doses (greater than or equal to 1 g/day) of niacin or nicotinic acid
- large quantities of grapefruit juice (>1 quart daily)

It is also important to tell your doctor if you are taking coumarin anticoagulants (drugs that prevent blood clots, such as warfarin).

Tell your doctor about any prescription and nonprescription medicines you are taking or plan to take, including natural or herbal remedies.

Tell your doctor about all your medical conditions including allergies.

Tell your doctor if you:

- drink substantial quantities of alcohol or ever had liver problems. VYTORIN may not be right for you.
- are pregnant or plan to become pregnant. Do not use VYTORIN if you are pregnant, trying to become pregnant or suspect that you are pregnant. If you become pregnant while taking VYTORIN, stop taking it and contact your doctor immediately.
- are breast-feeding. Do not use VYTORIN if you are breast-feeding.

Tell other doctors prescribing a new medication that you are taking VYTORIN.

How should I take VYTORIN?

Your doctor has prescribed your dose of VYTORIN. The available doses of VYTORIN are

10/10, 10/20, 10/40, and 10/80. The usual daily starting dose is VYTORIN 10/20.

- Take VYTORIN once a day, in the evening, with or without food.
- Try to take VYTORIN as prescribed. If you miss a dose, do not take an extra dose. Just resume your usual schedule.
- Continue to follow a cholesterol-lowering diet while taking VYTORIN. Ask your doctor if you need diet information.
- Keep taking VYTORIN unless your doctor tells you to stop. If you stop taking VYTORIN, your cholesterol may rise again.

What should I do in case of an overdose?

Contact your doctor immediately.

What are the possible side effects of VYTORIN?

See your doctor regularly to check your cholesterol level and to check for side effects. Your doctor may do blood tests to check your liver before you start taking VYTORIN and during treatment.

In clinical studies patients reported the following common side effects while taking VYTORIN: headache and muscle pain (see What should I tell my doctor before and while taking VYTORIN?).

The following side effects have been reported in general use with either ezetimibe or simvastatin tablets (tablets that contain the active ingredients of VYTORIN):

- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing (which may require treatment right away), rash, hives; joint pain; muscle pain; alterations in some laboratory blood tests; liver problems (sometimes serious); inflammation of the pancreas; nausea; dizziness; depression; gallstones; inflammation of the gallbladder.

Tell your doctor if you are having these or any other medical problems while on VYTORIN. This is not a complete list of side effects. For a complete list, ask your doctor or pharmacist.

What should I know about high cholesterol?

Cholesterol is a type of fat found in your blood. Cholesterol comes from two sources. It is produced by your body and it comes from the food you eat. Your total cholesterol is made up of both LDL and HDL cholesterol.

LDL cholesterol is called "bad" cholesterol because it can build up in the wall of your arteries and form plaque. Over time, plaque build-up can cause a narrowing of the arteries. This narrowing can slow or block blood flow to your heart, brain, and other organs. High LDL cholesterol is a major cause of heart disease and stroke.

HDL cholesterol is called "good" cholesterol because it keeps the bad cholesterol from building up in the arteries.

Triglycerides also are fats found in your body.

General Information about VYTORIN

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use VYTORIN for a condition for which it was not prescribed. Do not give VYTORIN to other people, even if they have the same condition you have. It may harm them.

This summarizes the most important information about VYTORIN. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about VYTORIN that is written for health professionals. For additional information, visit the following web site: vytorin.com.

Inactive ingredients:

Butylated hydroxyanisole NF, citric acid monohydrate USP, croscarmellose sodium NF, hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF,

microcrystalline cellulose NF, and propyl gallate NF.

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Manufactured for:

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REV 14

ZETIA(R)
(EZETIMIBE)
TABLETS

DESCRIPTION

ZETIA (ezetimibe) is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-(3-(4-fluorophenyl)-3(S)-hydroxypropyl)-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is C₂₄H₂₁F₂NO₃. Its molecular weight is 409.4 and its structural formula is:

(GRAPHIC OMITTED)

Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163 degrees C and is stable at ambient temperature. ZETIA is available as a tablet for oral administration containing 10 mg of ezetimibe and the following inactive ingredients: croscarmellose sodium NF, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, povidone USP, and sodium lauryl sulfate NF.

CLINICAL PHARMACOLOGY

Background

Clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B), the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of high density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

ZETIA reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with

hypercholesterolemia. Administration of ZETIA with an HMG-CoA reductase inhibitor is effective in improving serum total-C, LDL-C, Apo B, TG, and HDL-C beyond either treatment alone. Administration of ZETIA with fenofibrate is effective in improving serum total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia as compared to either treatment alone. The effects of ezetimibe given either alone or in addition to an HMG-CoA reductase inhibitor or fenofibrate on cardiovascular morbidity and mortality have not been established.

Mode of Action

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. In a 2-week clinical study in 18 hypercholesterolemic patients, ZETIA inhibited intestinal cholesterol absorption by 54%, compared with placebo. ZETIA had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E (in a study of 113 patients), and did not impair adrenocortical steroid hormone production (in a study of 118 patients).

The cholesterol content of the liver is derived predominantly from three sources. The liver can synthesize cholesterol, take up cholesterol from the blood from circulating lipoproteins, or take up cholesterol absorbed by the small intestine. Intestinal cholesterol is derived primarily from cholesterol secreted in the bile and from dietary cholesterol.

Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing compounds (HMG-CoA reductase inhibitors, bile acid sequestrants (resins), fibric acid derivatives, and plant stanols). The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols.

Ezetimibe does not inhibit cholesterol synthesis in the liver, or increase bile acid excretion. Instead, ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of HMG-CoA reductase inhibitors and of fenofibrate (see CLINICAL STUDIES).

Pharmacokinetics

Absorption

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10-mg dose of ZETIA to fasted adults, mean ezetimibe peak plasma concentrations (C_{max}) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours (T_{max}). Ezetimibe-glucuronide mean C_{max} values of 45 to 71 ng/mL were achieved between 1 and 2 hours (T_{max}). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection. Ezetimibe has variable bioavailability; the coefficient of variation, based on inter-subject variability, was 35 to 60% for AUC values.

Effect of Food on Oral Absorption

Concomitant food administration (high fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ZETIA 10-mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high fat meals. ZETIA can be administered with or without food.

Distribution

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Metabolism and Excretion

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary and renal excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma

with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Following oral administration of ¹⁴C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Special Populations

Geriatric Patients

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (greater than or equal to 65 years) healthy subjects compared to younger subjects.

Pediatric Patients

In a multiple-dose study with ezetimibe given 10 mg once daily for 7 days, the absorption and metabolism of ezetimibe were similar in adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Gender

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

Race

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Black and Caucasian subjects. Studies in Asian subjects indicated that the pharmacokinetics of ezetimibe were similar to those seen in Caucasian subjects.

Hepatic Insufficiency

After a single 10-mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe were increased approximately 3- to 4-fold and 5- to 6-fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency, the mean AUC values for total ezetimibe and ezetimibe were increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients (see CONTRAINDICATIONS and PRECAUTIONS, Hepatic Insufficiency).

Renal Insufficiency

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl less than or equal to 30 mL/min/1.73 m²), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5-fold, compared to healthy subjects (n=9).

Drug Interactions (See also PRECAUTIONS, Drug Interactions)

ZETIA had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a "cocktail" study of twelve healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized

by these enzymes.

Warfarin: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. There have been post-marketing reports of increased International Normalized Ratio (INR) in patients who had ezetimibe added to warfarin. Most of these patients were also on other medications (See PRECAUTIONS, Drug Interactions).

Digoxin: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of digoxin and the ECG parameters (HR, PR, QT, and QTc intervals) in a study of twelve healthy adult males.

Gemfibrozil: In a study of twelve healthy adult males, concomitant administration of gemfibrozil (600 mg twice daily) significantly increased the oral bioavailability of total ezetimibe by a factor of 1.7. Ezetimibe (10 mg once daily) did not significantly affect the bioavailability of gemfibrozil.

Oral Contraceptives: Co-administration of ezetimibe (10 mg once daily) with oral contraceptives had no significant effect on the bioavailability of ethinyl estradiol or levonorgestrel in a study of eighteen healthy adult females.

Cimetidine: Multiple doses of cimetidine (400 mg twice daily) had no significant effect on the oral bioavailability of ezetimibe and total ezetimibe in a study of twelve healthy adults.

Antacids: In a study of twelve healthy adults, a single dose of antacid (Supralox(TM) 20 mL) administration had no significant effect on the oral bioavailability of total ezetimibe, ezetimibe-glucuronide, or ezetimibe based on AUC values. The Cmax value of total ezetimibe was decreased by 30%.

Glipizide: In a study of twelve healthy adult males, steady-state levels of ezetimibe (10 mg once daily) had no significant effect on the pharmacokinetics and pharmacodynamics of glipizide. A single dose of glipizide (10 mg) had no significant effect on the exposure to total ezetimibe or ezetimibe.

HMG-CoA Reductase Inhibitors: In studies of healthy hypercholesterolemic (LDL-C greater than or equal to 130 mg/dL) adult subjects, concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of either lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, or rosuvastatin. No significant effect on the bioavailability of total ezetimibe and ezetimibe was demonstrated by either lovastatin (20 mg once daily), pravastatin (20 mg once daily), atorvastatin (10 mg once daily), fluvastatin (20 mg once daily), or rosuvastatin (10 mg once daily). (See PRECAUTIONS, Skeletal Muscle.)

Fenofibrate: In a study of thirty-two healthy hypercholesterolemic (LDL-C greater than or equal to 130 mg/dL) adult subjects, concomitant fenofibrate (200 mg once daily) administration increased the mean Cmax and AUC values of total ezetimibe approximately 64% and 48%, respectively. Pharmacokinetics of fenofibrate were not significantly affected by ezetimibe (10 mg once daily).

Cholestyramine: In a study of forty healthy hypercholesterolemic (LDL-C greater than or equal to 130 mg/dL) adult subjects, concomitant cholestyramine (4 g twice daily) administration decreased the mean AUC values of total ezetimibe and ezetimibe approximately 55% and 80%, respectively.

Cyclosporine: In a study of eight post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 mL/min), stable doses of cyclosporine (75 to 150 mg twice daily) increased the mean AUC and Cmax values of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively, compared to a historical healthy control population (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m²) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of cyclosporine alone (see PRECAUTIONS, Drug Interactions).

ANIMAL PHARMACOLOGY

The hypocholesterolemic effect of ezetimibe was evaluated in cholesterol-fed Rhesus monkeys, dogs, rats, and mouse models of human cholesterol metabolism. Ezetimibe was

found to have an ED50 value of 0.5 (mu)g/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED50 values in dogs, rats, and mice were 7, 30, and 700 (mu)g/kg/day, respectively. These results are consistent with ZETIA being a potent cholesterol absorption inhibitor.

In a rat model, where the glucuronide metabolite of ezetimibe (SCH 60663) was administered intraduodenally, the metabolite was as potent as the parent compound (SCH 58235) in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug.

In 1-month studies in dogs given ezetimibe (0.03 to 300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14-day study in mice given ezetimibe (0.3 to 5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

A series of acute preclinical studies was performed to determine the selectivity of ZETIA for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of 14C-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethyl estradiol, or the fat-soluble vitamins A and D.

In 4- to 12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with HMG-CoA reductase inhibitors (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

CLINICAL STUDIES

Primary Hypercholesterolemia

ZETIA reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with hypercholesterolemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy.

ZETIA is effective in patients with hypercholesterolemia, in men and women, in younger and older patients, alone or administered with an HMG-CoA reductase inhibitor. Experience in pediatric and adolescent patients (ages 9 to 17) has been limited to patients with homozygous familial hypercholesterolemia (HoFH) or sitosterolemia.

Monotherapy

In two, multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, ZETIA significantly lowered total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to placebo (see Table 1). Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

Table 1
Response to ZETIA in Patients with Primary Hypercholesterolemia
(Mean(a) % Change from Untreated Baseline(b))

	Treatment group	N	Total-C	LDL-C	Apo B	TG(a)	HDL-C
Study 1(c)	Placebo	205	+1	+1	-1	-1	-1
	Ezetimibe	622	-12	-18	-15	-7	+1
Study 2(c)	Placebo	226	+1	+1	-1	+2	-2
	Ezetimibe	666	-12	-18	-16	-9	+1
Pooled Data(c) (Studies 1 & 2)	Placebo	431	0	+1	-2	0	-2
	Ezetimibe	1288	-13	-18	-16	-8	+1

(a) For triglycerides, median % change from baseline

(b) Baseline - on no lipid-lowering drug

(c) ZETIA significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to placebo.

Combination with HMG-CoA Reductase Inhibitors

ZETIA Added to On-going HMG-CoA Reductase Inhibitor Therapy

In a multicenter, double-blind, placebo-controlled, 8-week study, 769 patients with primary hypercholesterolemia, known coronary heart disease or multiple cardiovascular risk factors who were already receiving HMG-CoA reductase inhibitor monotherapy, but who had not met their NCEP ATP II target LDL-C goal were randomized to receive either ZETIA or placebo in addition to their on-going HMG-CoA reductase inhibitor therapy.

ZETIA, added to on-going HMG-CoA reductase inhibitor therapy, significantly lowered total-C, LDL-C, Apo B, and TG, and increased HDL-C compared with an HMG-CoA reductase inhibitor administered alone (see Table 2). LDL-C reductions induced by ZETIA were generally consistent across all HMG-CoA reductase inhibitors.

Table 2
Response to Addition of ZETIA to On-going HMG-CoA Reductase Inhibitor Therapy(a) in Patients with Hypercholesterolemia (Mean(b) % Change from Treated Baseline(c))

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG(b)	HDL-C
On-going HMG-CoA reductase inhibitor +Placebo(d)	390	-2	-4	-3	-3	+1
On-going HMG-CoA reductase inhibitor +ZETIA(d)	379	-17	-25	-19	-14	+3

(a) Patients receiving each HMG-CoA reductase inhibitor: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)

(b) For triglycerides, median % change from baseline

(c) Baseline - on an HMG-CoA reductase inhibitor alone.

(d) ZETIA + HMG-CoA reductase inhibitor significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to HMG-CoA reductase inhibitor alone.

ZETIA Initiated Concurrently with an HMG-CoA Reductase Inhibitor

In four, multicenter, double-blind, placebo-controlled, 12-week trials, in 2382 hypercholesterolemic patients, ZETIA or placebo was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin.

When all patients receiving ZETIA with an HMG-CoA reductase inhibitor were compared to all those receiving the corresponding HMG-CoA reductase inhibitor alone, ZETIA significantly lowered total-C, LDL-C, Apo B, and TG, and, with the exception of pravastatin, increased HDL-C compared to the HMG-CoA reductase inhibitor administered alone. LDL-C reductions induced by ZETIA were generally consistent across all HMG-CoA reductase inhibitors. (See footnote c, Tables 3 to 6.)

Table 3
Response to ZETIA and Atorvastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean(a) % Change from Untreated Baseline(b))

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG(a)	HDL-C
Placebo	60	+4	+4	+3	-6	+4
ZETIA	65	-14	-20	-15	-5	+4
Atorvastatin 10 mg	60	-26	-37	-28	-21	+6
ZETIA + Atorvastatin 10 mg	65	-38	-53	-43	-31	+9
Atorvastatin 20 mg	60	-30	-42	-34	-23	+4

ZETIA + Atorvastatin 20 mg	62	-39	-54	-44	-30	+9
Atorvastatin 40 mg	66	-32	-45	-37	-24	+4
ZETIA + Atorvastatin 40 mg	65	-42	-56	-45	-34	+5
Atorvastatin 80 mg	62	-40	-54	-46	-31	+3
ZETIA + Atorvastatin 80 mg	63	-46	-61	-50	-40	+7
Pooled data (All Atorvastatin Doses) (c)	248	-32	-44	-36	-24	+4
Pooled data (All ZETIA + Atorvastatin Doses) (c)	255	-41	-56	-45	-33	+7

- (a) For triglycerides, median % change from baseline
(b) Baseline - on no lipid-lowering drug
(c) ZETIA + all doses of atorvastatin pooled (10-80 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of atorvastatin pooled (10-80 mg).

Table 4
Response to ZETIA and Simvastatin Initiated Concurrently
in Patients with Primary Hypercholesterolemia
(Mean(a) % Change from Untreated Baseline(b))

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG(a)	HDL-C
Placebo	70	-1	-1	0	+2	+1
ZETIA	61	-13	-19	-14	-11	+5
Simvastatin 10 mg	70	-18	-27	-21	-14	+8
ZETIA + Simvastatin 10 mg	67	-32	-46	-35	-26	+9
Simvastatin 20 mg	61	-26	-36	-29	-18	+6
ZETIA + Simvastatin 20 mg	69	-33	-46	-36	-25	+9
Simvastatin 40 mg	65	-27	-38	-32	-24	+6
ZETIA + Simvastatin 40 mg	73	-40	-56	-45	-32	+11
Simvastatin 80 mg	67	-32	-45	-37	-23	+8
ZETIA + Simvastatin 80 mg	65	-41	-58	-47	-31	+8
Pooled data (All Simvastatin Doses) (c)	263	-26	-36	-30	-20	+7
Pooled data (All ZETIA + Simvastatin Doses) (c)	274	-37	-51	-41	-29	+9

- (a) For triglycerides, median % change from baseline
(b) Baseline - on no lipid-lowering drug
(c) ZETIA + all doses of simvastatin pooled (10-80 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of simvastatin pooled (10-80 mg).

Table 5

Response to ZETIA and Pravastatin Initiated Concurrently
in Patients with Primary Hypercholesterolemia
(Mean(a) % Change from Untreated Baseline(b))

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG(a)	HDL-C
Placebo	65	0	-1	-2	-1	+2
ZETIA	64	-13	-20	-15	-5	+4
Pravastatin 10 mg	66	-15	-21	-16	-14	+6
ZETIA + Pravastatin 10 mg	71	-24	-34	-27	-23	+8
Pravastatin 20 mg	69	-15	-23	-18	-8	+8
ZETIA + Pravastatin 20 mg	66	-27	-40	-31	-21	+8
Pravastatin 40 mg	70	-22	-31	-26	-19	+6
ZETIA + Pravastatin 40 mg	67	-30	-42	-32	-21	+8
Pooled data (All Pravastatin Doses)(c)	205	-17	-25	-20	-14	+7
Pooled data (All ZETIA + Pravastatin Doses)(c)	204	-27	-39	-30	-21	+8

- (a) For triglycerides, median % change from baseline
(b) Baseline - on no lipid-lowering drug
(c) ZETIA + all doses of pravastatin pooled (10-40 mg) significantly reduced total-C, LDL-C, Apo B, and TG compared to all doses of pravastatin pooled (10-40 mg).

Table 6
Response to ZETIA and Lovastatin Initiated Concurrently
in Patients with Primary Hypercholesterolemia
(Mean(a) % Change from Untreated Baseline(b))

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG(a)	HDL-C
Placebo	64	+1	0	+1	+6	0
ZETIA	72	-13	-19	-14	-5	+3
Lovastatin 10 mg	73	-15	-20	-17	-11	+5
ZETIA + Lovastatin 10 mg	65	-24	-34	-27	-19	+8
Lovastatin 20 mg	74	-19	-26	-21	-12	+3
ZETIA + Lovastatin 20 mg	62	-29	-41	-34	-27	+9
Lovastatin 40 mg	73	-21	-30	-25	-15	+5
ZETIA + Lovastatin 40 mg	65	-33	-46	-38	-27	+9
Pooled data (All Lovastatin Doses)(c)	220	-18	-25	-21	-12	+4
Pooled data (All ZETIA + Lovastatin Doses)(c)	192	-29	-40	-33	-25	+9

- (a) For triglycerides, median % change from baseline

- (b) Baseline - on no lipid-lowering drug
- (c) ZETIA + all doses of lovastatin pooled (10-40 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of lovastatin pooled (10-40 mg).

Combination with Fenofibrate

In a multicenter, double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidemia, 625 patients were treated for up to 12 weeks and 576 for up to an additional 48 weeks. Patients were randomized to receive placebo, ZETIA alone, 160 mg fenofibrate alone, or ZETIA and 160 mg fenofibrate in the 12-week study. After completing the 12-week study, eligible patients were assigned to ZETIA co-administered with fenofibrate or fenofibrate monotherapy for an additional 48 weeks.

ZETIA co-administered with fenofibrate significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to fenofibrate administered alone. The percent decrease in TG and percent increase in HDL-C for ZETIA co-administered with fenofibrate were comparable to those for fenofibrate administered alone (see Table 7).

Table 7
Response to ZETIA and Fenofibrate Initiated Concurrently
in Patients with Mixed Hyperlipidemia
(Mean(a) % Change from Untreated Baseline(b) at 12 weeks)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG(a)	HDL-C	Non-HDL-C
Placebo	63	0	0	-1	-9	+3	0
ZETIA	185	-12	-13	-11	-11	+4	-15
Fenofibrate 160 mg	188	-11	-6	-15	-43	+19	-16
ZETIA + Fenofibrate 160 mg	183	-22	-20	-26	-44	+19	-30

(a) For triglycerides, median % change from baseline

(b) Baseline - on no lipid-lowering drug

The changes in lipid endpoints after an additional 48 weeks of treatment with ZETIA co-administered with fenofibrate or with fenofibrate alone were consistent with the 12-week data displayed above.

Homozygous Familial Hypercholesterolemia (HoFH)

A study was conducted to assess the efficacy of ZETIA in the treatment of HoFH. This double-blind, randomized, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HoFH, with or without concomitant LDL apheresis, already receiving atorvastatin or simvastatin (40 mg). Patients were randomized to one of three treatment groups, atorvastatin or simvastatin (80 mg), ZETIA administered with atorvastatin or simvastatin (40 mg), or ZETIA administered with atorvastatin or simvastatin (80 mg). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine (see PRECAUTIONS), ezetimibe was dosed at least 4 hours before or after administration of resins. Mean baseline LDL-C was 341 mg/dL in those patients randomized to atorvastatin 80 mg or simvastatin 80 mg alone and 316 mg/dL in the group randomized to ZETIA plus atorvastatin 40 or 80 mg or simvastatin 40 or 80 mg. ZETIA, administered with atorvastatin or simvastatin (40 and 80 mg statin groups, pooled), significantly reduced LDL-C (21%) compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg (7%). In those treated with ZETIA plus 80 mg atorvastatin or with ZETIA plus 80 mg simvastatin, LDL-C was reduced by 27%.

Homozygous Sitosterolemia (Phytosterolemia)

A study was conducted to assess the efficacy of ZETIA in the treatment of homozygous sitosterolemia. In this multicenter, double-blind, placebo-controlled, 8-week trial, 37 patients with homozygous sitosterolemia with elevated plasma sitosterol levels (>5 mg/dL) on their current therapeutic regimen (diet, bile-acid-binding resins, HMG-CoA reductase inhibitors, ileal bypass surgery and/or LDL apheresis), were randomized to receive ZETIA (n=30) or placebo (n=7). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine (see PRECAUTIONS), ezetimibe was dosed at least 2 hours before or 4 hours after resins were administered. Excluding the one subject receiving LDL apheresis, ZETIA significantly lowered plasma sitosterol and campesterol, by 21% and 24% from baseline, respectively. In contrast, patients who received placebo had increases in sitosterol and campesterol of 4% and 3% from

baseline, respectively. For patients treated with ZETIA, mean plasma levels of plant sterols were reduced progressively over the course of the study. The effects of reducing plasma sitosterol and campesterol on reducing the risks of cardiovascular morbidity and mortality have not been established.

Reductions in sitosterol and campesterol were consistent between patients taking ZETIA concomitantly with bile acid sequestrants (n=8) and patients not on concomitant bile acid sequestrant therapy (n=21).

INDICATIONS AND USAGE

Primary Hypercholesterolemia

Monotherapy

ZETIA, administered alone, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Combination Therapy with HMG-CoA Reductase Inhibitors

ZETIA, administered in combination with an HMG-CoA reductase inhibitor, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Combination Therapy with Fenofibrate

ZETIA, administered in combination with fenofibrate, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia.

Homozygous Familial Hypercholesterolemia (HoFH)

The combination of ZETIA and atorvastatin or simvastatin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Homozygous Sitosterolemia

ZETIA is indicated as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Therapy with lipid-altering agents should be a component of multiple risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to an appropriate diet (including restriction of saturated fat and cholesterol) and when the response to diet and other non-pharmacological measures has been inadequate. (See NCEP Adult Treatment Panel (ATP) III Guidelines, summarized in Table 8.)

Table 8
Summary of NCEP ATP III Guidelines

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes(a) (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents(b) (10-year risk >20%)(c)	<100	greater than or equal to 100	greater than or equal to 130 (100-129: drug optional)(d)
2+ Risk factors(e) (10-year risk less than or equal to 20%)(c)	<130	greater than or equal to 130	10-year risk 10-20%: greater than or equal to 130(c) 10-year risk <10%: greater than or equal to 160(c)

			greater than or equal to
0-1 Risk factor(f)	<160	greater than or	190
		equal to 160	(160-189: LDL-lowering drug optional)

(a) Therapeutic lifestyle changes include: 1) dietary changes: reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg per day), and enhancing LDL lowering with plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10-25 g/d), 2) weight reduction, and 3) increased physical activity.

(b) CHD risk equivalents comprise: diabetes, multiple risk factors that confer a 10-year risk for CHD >20%, and other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm and symptomatic carotid artery disease).

(c) Risk assessment for determining the 10-year risk for developing CHD is carried out using the Framingham risk scoring. Refer to JAMA, May 16, 2001; 285 (19): 2486-2497, or the NCEP website (<http://www.nhlbi.nih.gov>) for more details.

(d) Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

(e) Major risk factors (exclusive of LDL cholesterol) that modify LDL goals include cigarette smoking, hypertension (BP greater than or equal to 140/90 mm Hg or on anti-hypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), age (men greater than or equal to 45 years; women greater than or equal to 55 years). HDL cholesterol greater than or equal to 60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

(f) Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Prior to initiating therapy with ZETIA, secondary causes for dyslipidemia (i.e., diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C (progestins, anabolic steroids, and corticosteroids)), should be excluded or, if appropriate, treated. A lipid profile should be performed to measure total-C, LDL-C, HDL-C and TG. For TG levels >400 mg/dL (>4.5 mmol/L), LDL-C concentrations should be determined by ultracentrifugation.

At the time of hospitalization for an acute coronary event, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

The combination of ZETIA with an HMG-CoA reductase inhibitor is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When ZETIA is administered with an HMG-CoA reductase inhibitor in a woman of childbearing potential, refer to the pregnancy category and product labeling for the HMG-CoA reductase inhibitor. (See PRECAUTIONS, Pregnancy.)

PRECAUTIONS

Concurrent administration of ZETIA with a specific HMG-CoA reductase inhibitor or fenofibrate should be in accordance with the product labeling for that medication.

Liver Enzymes

In controlled clinical monotherapy studies, the incidence of consecutive elevations (greater than or equal to 3 X the upper limit of normal (ULN)) in serum transaminases was similar between ZETIA (0.5%) and placebo (0.3%).

In controlled clinical combination studies of ZETIA initiated concurrently with an HMG-CoA

reductase inhibitor, the incidence of consecutive elevations (greater than or equal to 3 X ULN) in serum transaminases was 1.3% for patients treated with ZETIA administered with HMG-CoA reductase inhibitors and 0.4% for patients treated with HMG-CoA reductase inhibitors alone. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. When ZETIA is co-administered with an HMG-CoA reductase inhibitor, liver function tests should be performed at initiation of therapy and according to the recommendations of the HMG-CoA reductase inhibitor.

Skeletal Muscle

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ZETIA compared with the relevant control arm (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipid-lowering drugs. In clinical trials, the incidence of CPK >10 X ULN was 0.2% for ZETIA vs 0.1% for placebo, and 0.1% for ZETIA co-administered with an HMG-CoA reductase inhibitor vs 0.4% for HMG-CoA reductase inhibitors alone.

In post-marketing experience with ZETIA, cases of myopathy and rhabdomyolysis have been reported regardless of causality. Most patients who developed rhabdomyolysis were taking an HMG-CoA reductase inhibitor prior to initiating ZETIA. However, rhabdomyolysis has been reported very rarely with ZETIA monotherapy and very rarely with the addition of ZETIA to agents known to be associated with increased risk of rhabdomyolysis, such as fibrates. All patients starting therapy with ezetimibe should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. ZETIA and any HMG-CoA reductase inhibitor or fibrate that the patient is taking concomitantly should be immediately discontinued if myopathy is diagnosed or suspected. The presence of these symptoms and a creatine phosphokinase (CPK) level >10 times the ULN indicates myopathy.

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients. (See CLINICAL PHARMACOLOGY, Special Populations.)

Drug Interactions (See also CLINICAL PHARMACOLOGY, Drug Interactions)

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction.

Fibrates: The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see ANIMAL PHARMACOLOGY). Co-administration of ZETIA with fibrates other than fenofibrate is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. If cholelithiasis is suspected in a patient receiving ZETIA and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered (see ADVERSE REACTIONS and the product labeling for fenofibrate).

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. No clinical data are available.

HMG-CoA Reductase Inhibitors: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

Cyclosporine: Caution should be exercised when using ZETIA and cyclosporine concomitantly due to increased exposure to both ezetimibe and cyclosporine. Cyclosporine concentrations should be monitored in patients receiving ZETIA and cyclosporine.

The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed

against the benefits of alterations in lipid levels provided by ezetimibe. In a pharmacokinetic study in post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 mL/min), concomitant cyclosporine administration increased the mean AUC and C_{max} of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively. In a separate study, the total ezetimibe exposure increased 12-fold in one renal transplant patient with severe renal insufficiency receiving multiple medications, including cyclosporine (see CLINICAL PHARMACOLOGY, Drug Interactions).

Warfarin: If ezetimibe is added to warfarin, the International Normalized Ratio should be appropriately monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on AUC(0-24hr) for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on AUC(0-24hr) for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed in vitro in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed in vitro in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the in vivo mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on AUC(0-24hr) for total ezetimibe).

Pregnancy

Pregnancy Category: C

There are no adequate and well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 times the human exposure at 10 mg daily based on AUC(0-24hr) for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 times the human exposure at 10 mg daily based on AUC(0-24hr) for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple-dose studies of ezetimibe given in combination with HMG-CoA reductase inhibitors (statins) in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in combination therapy compared to monotherapy.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When ZETIA is administered with an HMG-CoA reductase inhibitor in a woman of childbearing potential, refer to the pregnancy category and product labeling for the HMG-CoA reductase inhibitor. (See CONTRAINDICATIONS.)

Labor and Delivery

The effects of ZETIA on labor and delivery in pregnant women are unknown.

Nursing Mothers

In rat studies, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe is excreted into human breast milk; therefore, ZETIA should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

Pediatric Use

The pharmacokinetics of ZETIA in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ZETIA in the pediatric population is limited to 4 patients (9 to 17 years) in the sitosterolemia study and 5 patients (11 to 17 years) in the HoFH study. Treatment with ZETIA in children (<10 years) is not recommended. (See CLINICAL PHARMACOLOGY, Special Populations.)

Geriatric Use

Of the patients who received ZETIA in clinical studies, 948 were 65 and older (this included 206 who were 75 and older). The effectiveness and safety of ZETIA were similar between these patients and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, Special Populations and ADVERSE REACTIONS.)

ADVERSE REACTIONS

ZETIA has been evaluated for safety in more than 4700 patients in clinical trials. Clinical studies of ZETIA (administered alone or with an HMG-CoA reductase inhibitor) demonstrated that ZETIA was generally well tolerated. The overall incidence of adverse events reported with ZETIA was similar to that reported with placebo, and the discontinuation rate due to adverse events was also similar for ZETIA and placebo.

Monotherapy

Adverse experiences reported in greater than or equal to 2% of patients treated with ZETIA and at an incidence greater than placebo in placebo-controlled studies of ZETIA, regardless of causality assessment, are shown in Table 9.

Table 9*
Clinical Adverse Events Occurring in greater than or equal to 2% of
Patients Treated with ZETIA and at an Incidence Greater than Placebo,
Regardless of Causality

Body System/Organ Class Adverse Event	Placebo (%) n = 795	ZETIA 10 mg (%) n = 1691

Body as a whole - general disorders		
Fatigue	1.8	2.2
Gastro-intestinal system disorders		
Abdominal pain	2.8	3.0
Diarrhea	3.0	3.7
Infection and infestations		
Infection viral	1.8	2.2
Pharyngitis	2.1	2.3
Sinusitis	2.8	3.6
Musculo-skeletal system disorders		
Arthralgia	3.4	3.8
Back pain	3.9	4.1
Respiratory system disorders		
Coughing	2.1	2.3

*Includes patients who received placebo or ZETIA alone reported in Table 10.

The frequency of less common adverse events was comparable between ZETIA and placebo.

Combination with an HMG-CoA Reductase Inhibitor

ZETIA has been evaluated for safety in combination studies in more than 2000 patients.

In general, adverse experiences were similar between ZETIA administered with HMG-CoA reductase inhibitors and HMG-CoA reductase inhibitors alone. However, the frequency of increased transaminases was slightly higher in patients receiving ZETIA administered with HMG-CoA reductase inhibitors than in patients treated with HMG-CoA reductase inhibitors alone. (See PRECAUTIONS, Liver Enzymes.)

Clinical adverse experiences reported in greater than or equal to 2% of patients and at an

incidence greater than placebo in four placebo-controlled trials where ZETIA was administered alone or initiated concurrently with various HMG-CoA reductase inhibitors, regardless of causality assessment, are shown in Table 10.

Table 10*
Clinical Adverse Events occurring in
greater than or equal to 2% of Patients and at an Incidence Greater
than Placebo, Regardless of Causality, in ZETIA/Statin Combination
Studies

Body System/Organ Class	Placebo (%) n=259	ZETIA 10 mg (%) n=262	All Statins** (%) n=936	ZETIA + All Statins** (%) n=925

Adverse Event	(%) n=259	(%) n=262	(%) n=936	(%) n=925

Body as a whole - general disorders				
Chest pain	1.2	3.4	2.0	1.8
Dizziness	1.2	2.7	1.4	1.8
Fatigue	1.9	1.9	1.4	2.8
Headache	5.4	8.0	7.3	6.3
Gastro-intestinal system disorders				
Abdominal pain	2.3	2.7	3.1	3.5
Diarrhea	1.5	3.4	2.9	2.8
Infection and infestations				
Pharyngitis	1.9	3.1	2.5	2.3
Sinusitis	1.9	4.6	3.6	3.5
Upper respiratory tract infection	10.8	13.0	13.6	11.8
Musculo-skeletal system disorders				
Arthralgia	2.3	3.8	4.3	3.4
Back pain	3.5	3.4	3.7	4.3
Myalgia	4.6	5.0	4.1	4.5

*Includes four placebo-controlled combination studies in which ZETIA was initiated concurrently with an HMG-CoA reductase inhibitor.

**All Statins = all doses of all HMG-CoA reductase inhibitors.

Combination with Fenofibrate

In a clinical study involving 625 patients treated for up to 12 weeks and 576 patients treated for up to an additional 48 weeks, co-administration of ZETIA and fenofibrate was well tolerated. This study was not designed to compare treatment groups for infrequent events. Incidence rates (95% CI) for clinically important elevations (> 3 X ULN, consecutive) in serum transaminases were 4.5% (1.9, 8.8) and 2.7% (1.2, 5.4) for fenofibrate monotherapy and ZETIA co-administered with fenofibrate, respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0.6% (0.0, 3.1) and 1.7% (0.6, 4.0) for fenofibrate monotherapy and ZETIA co-administered with fenofibrate, respectively (see PRECAUTIONS, Drug Interactions). The numbers of patients exposed to co-administration therapy as well as fenofibrate and ezetimibe monotherapy were inadequate to assess gallbladder disease risk. There were no CPK elevations > 10 X ULN in any of the treatment groups.

Post-marketing Experience

The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment:

Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria; arthralgia; myalgia; elevated creatine phosphokinase; myopathy/rhabdomyolysis (very rarely; see PRECAUTIONS, Skeletal Muscle); elevations in liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; dizziness; depression; cholelithiasis; cholecystitis.

OVERDOSAGE

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, was generally well tolerated.

A few cases of overdosage with ZETIA have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ZETIA and should continue on this diet during treatment with ZETIA.

The recommended dose of ZETIA is 10 mg once daily. ZETIA can be administered with or without food.

ZETIA may be administered with an HMG-CoA reductase inhibitor (in patients with primary hypercholesterolemia) or with fenofibrate (in patients with mixed hyperlipidemia) for incremental effect. For convenience, the daily dose of ZETIA may be taken at the same time as the HMG-CoA reductase inhibitor or fenofibrate, according to the dosing recommendations for the respective medications.

Patients with Hepatic Insufficiency

No dosage adjustment is necessary in patients with mild hepatic insufficiency (see PRECAUTIONS, Hepatic Insufficiency).

Patients with Renal Insufficiency

No dosage adjustment is necessary in patients with renal insufficiency (see CLINICAL PHARMACOLOGY, Special Populations).

Geriatric Patients

No dosage adjustment is necessary in geriatric patients (see CLINICAL PHARMACOLOGY, Special Populations).

Co-administration with Bile Acid Sequestrants

Dosing of ZETIA should occur either greater than or equal to 2 hours before or greater than or equal to 4 hours after administration of a bile acid sequestrant (see PRECAUTIONS, Drug Interactions).

HOW SUPPLIED

No. 3861 - Tablets ZETIA, 10 mg, are white to off-white, capsule-shaped tablets debossed with "414" on one side. They are supplied as follows:

NDC 66582-414-31 bottles of 30
NDC 66582-414-54 bottles of 90
NDC 66582-414-74 bottles of 500
NDC 66582-414-28 unit dose packages of 100.

Storage

Store at 25 degrees C (77 degrees F); excursions permitted to 15-30 degrees C (59-86 degrees F). (See USP Controlled Room Temperature.) Protect from moisture.

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ZETIA(R) (ezetimibe) Tablets

Patient Information about ZETIA (zet'-e-a)
Generic name: ezetimibe (e-zet'-e-mib)

Read this information carefully before you start taking ZETIA and each time you get more ZETIA. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about ZETIA, ask your doctor. Only your doctor can determine if ZETIA is right for you.

What is ZETIA?

ZETIA is a medicine used to lower levels of total cholesterol and LDL (bad) cholesterol in the blood. It is used for patients who cannot control their cholesterol levels by diet alone. It can be used by itself or with other medicines to treat high cholesterol. You should stay on a cholesterol-lowering diet while taking this medicine.

ZETIA works to reduce the amount of cholesterol your body absorbs. ZETIA does not help you lose weight.

For more information about cholesterol, see the "What should I know about high cholesterol?" section that follows.

Who should not take ZETIA?

- Do not take ZETIA if you are allergic to ezetimibe, the active ingredient in ZETIA, or to the inactive ingredients. For a list of inactive ingredients, see the "Inactive ingredients" section that follows.
- If you have active liver disease, do not take ZETIA while taking cholesterol-lowering medicines called statins.
- If you are pregnant or breast-feeding, do not take ZETIA while taking a statin.

What should I tell my doctor before and while taking ZETIA?

Tell your doctor about any prescription and non-prescription medicines you are taking or plan to take, including natural or herbal remedies.

Tell your doctor about all your medical conditions including allergies.

Tell your doctor if you:

- ever had liver problems. ZETIA may not be right for you.
- are pregnant or plan to become pregnant. Your doctor will decide if ZETIA is right for you.
- are breast-feeding. We do not know if ZETIA can pass to your baby through your milk. Your doctor will decide if ZETIA is right for you.
- experience unexplained muscle pain, tenderness, or weakness.

How should I take ZETIA?

- Take ZETIA once a day, with or without food. It may be easier to remember to take your dose if you do it at the same time every day, such as with breakfast, dinner, or at bedtime. If you also take another medicine to reduce your cholesterol, ask your doctor if you can take them at the same time.
- If you forget to take ZETIA, take it as soon as you remember. However, do not take more than one dose of ZETIA a day.
- Continue to follow a cholesterol-lowering diet while taking ZETIA. Ask your doctor if you need diet information.
- Keep taking ZETIA unless your doctor tells you to stop. It is important that you keep taking ZETIA even if you do not feel sick.

See your doctor regularly to check your cholesterol level and to check for side effects.

Your doctor may do blood tests to check your liver before you start taking ZETIA with a statin and during treatment.

What are the possible side effects of ZETIA?

In clinical studies patients reported few side effects while taking ZETIA. These included stomach pain and feeling tired.

Very rarely, patients have experienced severe muscle problems while taking ZETIA, usually when ZETIA was added to a statin drug. If you experience unexplained muscle pain, tenderness, or weakness while taking ZETIA, contact your doctor immediately. You need to do this promptly, because on rare occasions, these muscle problems can be serious, with muscle breakdown resulting in kidney damage.

Additionally, the following side effects have been reported in general use: allergic reactions (which may require treatment right away) including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing, rash, and hives; joint pain; muscle aches; alterations in some laboratory blood tests; liver problems; inflammation of the pancreas; nausea; dizziness; depression; gallstones; inflammation of the gallbladder.

Tell your doctor if you are having these or any other medical problems while on ZETIA. For a complete list of side effects, ask your doctor or pharmacist.

What should I know about high cholesterol?

Cholesterol is a type of fat found in your blood. Your total cholesterol is made up of LDL and HDL cholesterol.

LDL cholesterol is called "bad" cholesterol because it can build up in the wall of your arteries and form plaque. Over time, plaque build-up can cause a narrowing of the arteries. This narrowing can slow or block blood flow to your heart, brain, and other organs. High LDL cholesterol is a major cause of heart disease and stroke.

HDL cholesterol is called "good" cholesterol because it keeps the bad cholesterol from building up in the arteries.

Triglycerides also are fats found in your blood.

General information about ZETIA

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use ZETIA for a condition for which it was not prescribed. Do not give ZETIA to other people, even if they have the same condition you have. It may harm them.

This summarizes the most important information about ZETIA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ZETIA that is written for health professionals.

Inactive ingredients:

Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

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