Tool Kit for Faster D2B Times Involves Simple Changes

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CHICAGO — At the heart of the new national campaign to reduce hospital door-to-balloon times for patients with ST-elevation MI undergoing primary percutaneous intervention is a tool kit designed to help participating hospitals boost performance.

"It's simple, easy to implement, concise, and spans a number of different processes in the hospital that we need to improve," Dr. Wayne B. Batchelor explained at the annual scientific sessions of the American Heart Association.

Dr. Batchelor, an interventional cardiologist at Tallahassee (Fla.) Memorial Hospital who helped develop the tool kit, knows from firsthand experience that it works. "We found when we implemented these changes that our door-to-balloon times came down from around 110 minutes to …75-80 minutes. And we've seen with that a 36% drop in mortality in the space of about a year," he said. "We've also seen the proportion of ST-elevation MI patients who undergo primary PCI rise from about one-half to 95%-100% very quickly. … We've shaved more than a day off our median length of stay simply by getting patients treated earlier," Dr. Batchelor added.

Dr. Harlan M. Krumholz, chair of the Guidelines Applied in Practice–Door-to-Balloon (GAP-D2B) Working Group, said he knows of hospitals that have gotten their door-to-balloon times down into the 60- to 70-minute range using the key strategies promoted in the GAP-D2B campaign.

The GAP-D2B initiative is an example of a new, more proactive paradigm for translating potentially lifesaving academic research into clinical practice, added Dr. Krumholz, professor of medicine at Yale University, New Haven, Conn.

The campaign launch was tied to the release of a major study that provides evidence of the specific steps integral to getting D2B times of 90 minutes or less as recommended in national guidelines (see p. 1). "We're not going to be happy unless this campaign changes practice in the next 12 months," he said. ■

VYTORIN® (ezetimibe/simvastatin)
Brief Summary of Prescribing Information
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 × 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 × 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, and other fibrates: The safety and effectiveness of ezetimibe administered with fibrates have not been established. **Therefore, the concomitant use of VYTORIN and fibrates should be avoided.**
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 PRECAUTIONS, *Drug Interactions*, *Other drug interactions, Fibrates.)*
Niacin (≥1 g/day): Caution should be used when prescribing lipid-lowering doses (≥1 g/day) of niacin with VYTORIN, as niacin can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of VYTORIN with niacin should be carefully weighed against the potential risks of this drug combination** (see PRECAUTIONS, *Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone*).
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 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 the table below (see also PRECAUTIONS, *Drug Interactions*).
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.

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Liver Enzymes
In 3 placebo-controlled, 12-week trials, the incidence of consecutive elevations (≥3 × 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 (≥3 × 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 (eg, 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 × 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 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.
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*. Itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, 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
Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol particularly with higher doses of VYTORIN (see WARNINGS, *Myopathy/Rhabdomyolysis*).
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: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine particularly with higher doses of VYTORIN (see WARNINGS, *Myopathy/Rhabdomyolysis*).
Caution should be exercised when using VYTORIN and cyclosporine concomitantly due to increased exposure to both ezetimibe and cyclosporine. Cyclosporine concentrations should be monitored in patients receiving VYTORIN 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 WARNINGS, *Myopathy/Rhabdomyolysis*.)
Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (<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. 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 12 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

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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 2 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 3 months at 90 mg/kg/day (19 times) and at 2 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 $AUC_{0\text{-}24hr}$ 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 $AUC_{0\text{-}24hr}$ 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 $AUC_{0\text{-}24hr}$ 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 2-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 2-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-mg 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 $AUC_{0\text{-}24hr}$ 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 $AUC_{0\text{-}24hr}$ 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 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

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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 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 >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 ADVERSE REACTIONS.)
ADVERSE REACTIONS
VYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. VYTORIN was generally well tolerated.
The table below summarizes the frequency of clinical adverse experiences reported in ≥2% of patients treated with VYTORIN (n=1236) and at an incidence greater than placebo regardless of causality assessment from 3 similarly designed, placebo-controlled trials.
Clinical Adverse Events Occurring in ≥2% of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality*

Body System/ Organ Class Adverse Event	Placebo (%) n=311	Ezetimibe 10 mg (%) n=302	Simvastatin† (%) n=1234	VYTORIN† (%) 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 2 placebo-controlled combination studies in which the active ingredients equivalent to VYTORIN were coadministered and 1 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; elevations in liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; 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 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-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, and hepatoma.
Metabolism and nutrition disorders: anorexia.
Skin and subcutaneous tissue disorders: alopecia, pruritus. A variety of skin changes (eg, 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 1 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 PRECAUTIONS, *Pediatric Use*).

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