

Ezetimibe/Simvastatin (Vytorin[®]) Monograph¹⁻²**Brand Name:** Vytorin[®]**Generic Name:** Ezetimibe/Simvastatin**Manufacturer:** Merck/Schering Plough Pharmaceuticals**Year introduced:** FDA approved July 23, 2004**Mechanisms of Action:**

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol within the small intestine. The molecular target of ezetimibe has been shown to be the sterol transporter, NPC1L1, which is involved in the intestinal uptake of cholesterol and phytosterols. It localizes and acts at the brush border of the small intestine. The inhibition of cholesterol absorption leads 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.

Simvastatin reduces cholesterol by inhibiting the conversion of HMG CoA to mevalonate, an early step in the biosynthetic pathway for cholesterol. Simvastatin also reduces very-low-density lipoproteins (VLDL) and triglycerides (TG) and increases high-density lipoprotein cholesterol (HDL-C).

FDA-approved indications:

- Primary Hypercholesterolemia
- Homozygous Familial Hypercholesterolemia

Contraindications:

- Hypersensitivity to any component of the medication
- Active liver disease or unexplained persistent elevations in serum transaminases
- Pregnancy and lactation

Pharmacokinetics:

VYTORIN is bioequivalent to co-administered ezetimibe and simvastatin.

	<i>Ezetimibe</i>	<i>Simvastatin</i>
<i>Bioavailability:</i>	Variable bioavailability; the coefficient of variation, based on intersubject variability, was 35-60% for AUC values.	<5%
<i>Protein Binding:</i>	Ezetimibe and ezetimibe-glucuronide are highly protein bound (>90%).	Both simvastatin and its β -hydroxyacid metabolite are highly bound (~95%) to plasma proteins.

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	<i>Ezetimibe</i>	<i>Simvastatin</i>
<i>Metabolism:</i>	Extensive conjugation to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Metabolism takes place primarily in the small intestine and liver.	Simvastatin is an inactive prodrug that is hydrolyzed to the potent β -hydroxyacid metabolite and other active metabolites.
<i>Elimination:</i>	Biliary (~78%) and renal (~11%)	Fecal (60%) and renal (13%)
<i>Half-life:</i>	~22 hours (enterohepatic recycling)	1.9 hours

Adverse Effects:**Clinical Adverse Events Occurring in $\geq 2\%$ of Patients treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality***

Adverse Event (%)	Placebo	Ezetimibe	Simvastatin (all doses)	VYTORIN (all doses)
<i>Body as a Whole</i>				
Headache	6.4	6.0	5.9	6.8
<i>Infection and Infestations</i>				
Influenza	1.0	1.0	1.9	2.6
Upper Respiratory Tract Infection	2.6	5.0	5.0	3.9
<i>Musculoskeletal</i>				
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 co-administered and one placebo-controlled study in which VYTORIN was administered.

Other adverse experiences reported with ezetimibe in placebo-controlled studies and post-marketing experience (regardless of causality): abdominal pain, arthralgia, back pain, cholelithiasis, cholecystitis, coughing, diarrhea, elevations in liver transaminases, fatigue, hepatitis, hypersensitivity reactions (including angioedema, rash, urticaria, and arthralgia), increased CPK, myalgia, myopathy/rhabdomyolysis (very rarely), nausea, pancreatitis, pharyngitis, sinusitis, thrombocytopenia and viral infection.

Other adverse experiences reported with simvastatin in placebo-controlled clinical studies (regardless of causality): abdominal pain, asthenia, cataract, constipation, diarrhea, dyspepsia, eczema, flatulence, nausea, pruritus, and rash.

Drug Interactions:

Specific pharmacokinetic drug interaction studies with VYTORIN have not been performed.

Precipitant Drug	Object Drug	Effect	Description
Amiodarone	Simvastatin	↑	Increased risk of myopathy/rhabdomyolysis
Cholestyramine	Ezetimibe	↓	Cholestyramine administration decreased the mean AUC values of total ezetimibe approximately 55%.
Cyclosporine	Ezetimibe	↑	When ezetimibe was initiated in patients treated with cyclosporine, exposure to ezetimibe increased (2.3- to 7.9-fold increase in AUC and 3.0- to 4.4-fold increase in C _{max}).
Cyclosporine	Simvastatin	↑	Increased risk of myopathy/rhabdomyolysis. 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.
Danazol	Simvastatin	↑	Increased risk of myopathy/rhabdomyolysis
Ezetimibe	Cyclosporine	↑	When cyclosporine was administered to subjects receiving ezetimibe, changes in cyclosporine AUC (range: 10% decrease to 51% increase) occurred.
Fenofibrate	Ezetimibe	↑	Fenofibrate increased the mean C _{max} and AUC values for total ezetimibe approximately 65% and 48%, respectively.
Fenofibrate	Simvastatin	-	Coadministration of fenofibrate (160 mg/day) with simvastatin (80 mg/day) 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 of simvastatin acid, which was not considered clinically significant.
Gemfibrozil	Ezetimibe	↑	Gemfibrozil increased the oral bioavailability of ezetimibe by a factor of 1.7.
Gemfibrozil Other fibrates Niacin ≥1 g/day	Simvastatin	↑	Increased risk of myopathy/rhabdomyolysis; therefore, although not recommended, if VYTORIN is used in combination with gemfibrozil, the dose should not exceed 10/10 mg daily.
Grapefruit juice	Simvastatin	↑	Mean increase in the plasma concentration of active and total HMG-CoA reductase inhibitory activity
Potent inhibitors of CYP3A4*	Simvastatin	↑	Increased risk of myopathy/rhabdomyolysis
Simvastatin	Digoxin	↑	Slight elevation in plasma concentrations
Simvastatin	Warfarin	↑	Increased prothrombin time (INR) from baseline
Verapamil	Simvastatin	↑	Increased risk of myopathy/rhabdomyolysis

* Examples of potent CYP3A4 inhibitors: Cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone or large quantities of grapefruit juice [>1 quart daily]

Precaution/Warnings:Myopathy/Rhabdomyolysis

- Simvastatin, like other HMG-CoA reductase inhibitors, may cause myopathy. The risk of myopathy is increased when it is used concomitantly with potent inhibitors of cytochrome P450 3A4. Therefore, the use of VYTORIN concomitantly with the following inhibitors of CYP3A4 should be avoided: itraconazole, ketoconazole, erythromycin, clarithromycin,

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telithromycin, HIV protease inhibitors, nefazodone, and large quantities of grapefruit juice [>1 quart daily]).

- There is an increased risk of myopathy when simvastatin is used concomitantly with fibrate; therefore, although not recommended, if VYTORIN is used in combination with gemfibrozil, the dose should not exceed 10/10 mg/day.
- The risk of myopathy/rhabdomyolysis with simvastatin is dose-related.
- The dose of VYTORIN should not exceed 10/10 mg daily in patients receiving cyclosporine or danazol.
- The dose of VYTORIN should not exceed 10/20 mg daily in patients receiving amiodarone or verapamil.
- 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.

Liver Enzymes/Hepatotoxicity

- In three placebo-controlled, 12-week trials, the incidence of consecutive elevations (≥ 3 x ULN) in serum transaminase was 1.7% overall for patients treated with VYTORIN. The incidence appeared to be dose-related as the incidence for patients treated with VYTORIN 10/80 was 2.6%. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.
- VYTORIN should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. VYTORIN is contraindicated in active liver disease or unexplained persistent transaminase elevations.

Hypersensitivity Reactions

- Ezetimibe may cause allergic reactions, including angioedema (which can be fatal), rash, urticaria, and arthralgia.

Cholelithiasis

- In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Fibrates may increase cholesterol excretion in the bile, leading to cholelithiasis. Co-administration of VYTORIN with fibrates is not recommended.

CNS Toxicity

- Optic nerve degeneration was seen in clinically normal dogs treated for 14 weeks with a dose of simvastatin that produced mean plasma drug levels approximately 12 times higher than the mean plasma drug level in humans taking 80 mg/day.
- CNS vascular lesions were seen in dogs treated with a simvastatin dose that produced mean plasma drug levels approximately 14 times higher than the mean plasma drug level in humans taking 80 mg/day.
- 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).

Anaphylaxis

- Anaphylaxis has been reported in post-marketing experience.

Pregnancy/Lactation:

- Pregnancy Category X

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- 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 or simvastatin is excreted into human breast milk. Because a small amount of another HMG-CoA reductase inhibitor is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, VYTORIN should not be used in nursing mothers.

Usual Dosage:

- Dosage range: 10/10 mg/day to 10/80 mg/day.
- Recommended usual starting dose: 10/20 mg/day
- Starting dose for patients requiring less aggressive LDL-C reduction: 10/10 mg/day
- Starting dose for patients requiring a larger LDL-C reduction (>55%): 10/40 mg/day
- Dose either ≥ 2 hours before or ≥ 4 hours after administration with a bile acid sequestrant.
- Patients taking cyclosporine or danazol: Dose should not exceed 10/10 mg/day.
- Patients taking amiodarone or verapamil: Dose should not exceed 10/20 mg/day.
- The safety and efficacy of VYTORIN administered with fibrates have not been established; therefore, the combination of VYTORIN and fibrates should be avoided.

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Clinical Studies:

Title and Author	Study Design	Results
<p>Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia.</p> <p>Ballantyne AM, et al. ³</p> <p>2004</p>	<p>A multicenter, randomized, double-blind, active-controlled trial comparing the efficacy of statin monotherapy with the co-administration of ezetimibe and simvastatin in decreasing LDL-C.</p> <p>24 weeks of active treatment (four 6-week treatment periods)</p> <p>Patients (n=788) were randomized to 1 of 3 once daily treatments:</p> <ul style="list-style-type: none"> • Atorvastatin 10 mg titrated to 20 mg (week 7), 40 mg (week 13), and 80 mg (week 19) • Co-administration of 10/10 mg of ezetimibe + simvastatin titrated to 10/20 mg (week 7), 10/40 mg (week 13), and 10/80 mg (week 19) • Co-administration of 10/20 mg of ezetimibe + simvastatin titrated to 10/40 mg (week 13) and 10/80 mg (week 19) <p><u>Inclusion Criteria</u></p> <ul style="list-style-type: none"> • ≥18 years of age • LDL-C at or above NCEP ATP III drug treatment threshold • One of the following: <ol style="list-style-type: none"> 1) established CHD or its risk equivalent, or with ≥2 risk factors conferring a 10-year risk >20% for CHD, and an LDL-C ≥130 mg/dl; 2) no CHD or its risk equivalent, and with ≥2 risk factors conferring a 10-year risk <20% for CHD, 	<p>Primary endpoint:</p> <ul style="list-style-type: none"> • Mean percent change in LDL-C from baseline to the end of the initial 6-week treatment period (10/10 mg ezetimibe + simvastatin vs. 10mg atorvastatin) <p>Secondary endpoints:</p> <ul style="list-style-type: none"> • Percent change in LDL-C from baseline to the ends of the second and fourth 6-week periods; percent change in HDL-C from baseline to the end of the study; percent changes across the ezetimibe + simvastatin and atorvastatin dose ranges in other lipid parameters: apolipoprotein B, apolipoprotein A-1, apolipoprotein B/apolipoprotein A-1, TC, non-HDL-C, and TG • Safety variable: adverse events <p>Efficacy: ezetimibe + simvastatin > atorvastatin</p> <ul style="list-style-type: none"> • At the end of the first 6-week treatment period, 10/10 mg of ezetimibe + simvastatin was significantly more effective than 10 mg atorvastatin in decreasing direct LDL-C (-46.1% combination vs. -37.2% atorvastatin; difference -8.9, 95% CI -11.1 to -6.7, p<0.001). • 10/20 mg of ezetimibe + simvastatin resulted in a 50.3% decrease in LDL-C at week 6; this was also statistically different from 10mg atorvastatin (difference -13.1%; 95% CI -15.2 to -10.9; p<0.001). • Mean percent decreases in LDL-C were significantly greater (p≤0.05) for the combination therapy compared to the corresponding atorvastatin dose at time points measured: week 12 – atorvastatin 20 mg -44.3%, ezetimibe +simvastatin 10/20 mg -50.2%, ezetimibe +simvastatin 10/40 mg -54.3%; week 18 – atorvastatin 40 mg -49.1%, ezetimibe +simvastatin 10/40 mg -55.6%; week 24 atorvastatin 80 mg -52.5%, ezetimibe +simvastatin 10/80 mg -59.4%. • Mean HDL-C was significantly greater (p≤0.05) at week 6 for ezetimibe + simvastatin 10/10 mg (8.0%) and ezetimibe + simvastatin 10/20 mg (9.5%) compared to atorvastatin 10 mg (5.1%), at week 12 for ezetimibe + simvastatin 10/40 mg (12.4%) compared to atorvastatin 20 mg (6.9%), at week 18 for ezetimibe + simvastatin 10/40 mg (11.4%) compared to atorvastatin 40 mg (7.8%), and at week 24 for ezetimibe + simvastatin 10/80 mg (12.3%) compared to atorvastatin 80 mg (6.5%). • Ezetimibe + simvastatin significantly improved (p≤0.05) the following lipid parameters compared to atorvastatin: apolipoprotein B, apolipoprotein A-1, apolipoprotein B/apolipoprotein A-1, TC, and non-HDL-C. • Changes in TG did not differ significantly between treatment groups. <p>Safety: ezetimibe + simvastatin ≈ atorvastatin</p> <ul style="list-style-type: none"> • The safety profiles were similar across all groups. • Drug-related adverse events were reported for 16% of patients who received ezetimibe + simvastatin 10/10 mg as the start dose, 13.7% of patients who received ezetimibe + simvastatin 10/20 mg as the start dose, and 16% of patients who received atorvastatin 10 mg as the start dose. • Similar proportions of patients reported adverse events that resulted in treatment discontinuation (5.7% in both combination groups and 3.8% in the atorvastatin group).

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	<p>and an LDL-C ≥ 160 mg/dl; 3) no CHD or its risk equivalent with < 2 risk factors and with LDL-C ≥ 190 mg/dl</p> <ul style="list-style-type: none"> • TG ≤ 350 mg/dl • ALT and AST < 1.5 times ULN • SCr ≤ 1.5 mg/dl • No active liver disease • HbA_{1c} $< 9\%$ 	<ul style="list-style-type: none"> • All treatment groups had similar incidences of consecutive elevations ≥ 3 x ULN of ALT, AST, and ALT/AST. • There were no cases of rhabdomyolysis or increases in creatine kinase ≥ 10 x ULN.
<p>Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals.</p> <p>Feldman T, et al. ⁴</p> <p>2004</p>	<p>A multicenter, randomized, double-blind, parallel-group trial evaluating the efficacy of ezetimibe co-administered with simvastatin (10 to 40 mg) versus simvastatin alone in helping high-risk hypercholesterolemic patients achieve their NCEP ATP III LDL-C goal</p> <p>23 weeks of active treatment</p> <p>Patients (n=710) were randomized to 1 of 4 once daily treatments:</p> <ul style="list-style-type: none"> • Simvastatin 20 mg (S20) • Ezetimibe + simvastatin 10/10 mg (E10 + S10) • Ezetimibe + simvastatin 10/20 mg (E10 + S20) • Ezetimibe + simvastatin 10/40 mg (E10 + S40) <p>Patients remained on the initial dose of simvastatin for the first 6 weeks of the study. In all groups, the simvastatin doses were doubled at weeks 6, 12, and/or 18 up to 80 mg/day in patients who did not achieve the target LDL-C goal to < 100 mg/dl.</p> <p><u>Inclusion Criteria</u></p> <ul style="list-style-type: none"> • 18-80 years of age • CHD or CHD risk equivalent according to NCEP ATP III guidelines • Plasma LDL-C ≥ 130 	<p>Primary endpoint:</p> <ul style="list-style-type: none"> • Efficacy of ezetimibe + simvastatin 10/10 mg versus simvastatin 20 mg in attaining the target LDL-C goal of < 100 mg/dl after 5 weeks <p>Secondary endpoints:</p> <ul style="list-style-type: none"> • Goal attainment of ezetimibe + simvastatin 20 mg and 40 mg relative to simvastatin 20 mg; the percentage of patients attaining goal at the end of the study; the number of simvastatin dose titrations and the median simvastatin dose used throughout the study; the efficacy of ezetimibe + simvastatin versus simvastatin alone on other lipid parameters; safety and tolerability <p>Efficacy: ezetimibe + simvastatin > simvastatin</p> <ul style="list-style-type: none"> • At week 5, 75% of patients in the E10 + S10 group compared to 46% of patients in the S20 group achieved the LDL-C goal of < 100 mg/dl ($p < 0.001$). 83% of patients in the E10 + S20 group and 87% of patients in the E10 + S40 group attained the LDL-C goal (both $p < 0.001$ vs. S20). • The treatment effect was consistent across the subgroups for age, gender, and baseline LDL-C. Because of limited sample sizes, treatment-by-CHD category and treatment-by-race interaction tests were not performed. • At the end of the study, 59% of patients started on S20, 78% of patients started on E10 + S10, 83% of patients started on E10 + S20, and 86% of patients started on E10 + S40 attained the LDL-C goal ($p < 0.001$ for all combinations vs. simvastatin). • 68% of patients on simvastatin monotherapy, 33% of patients started on E10 + S10, 22% of patients started on E10 + S20, and 12% of patients started on E10 + S40 required dose titration ($p < 0.001$ for all combinations vs. S20). • The mean and median simvastatin doses, respectively, used in each group were 50.3 mg and 40 mg for the S20 group, 20.2 mg and 10 mg for the E10 + S10 group, 27.7 mg and 20 mg for the E10 + S20 group, and 44.9 and 40 mg for the E10 + S40 group ($p < 0.001$ for all combinations vs. S20). • Ezetimibe + simvastatin 10, 20, or 40 mg significantly improved the following lipid parameters compared to simvastatin 20mg at the end of the first treatment period: LDL-C, TC, non-HDL-C, apolipoprotein B, TC:HDL-C ratio, LDL-C:HDL-C ratio (all $p < 0.001$); TG (only E10+ S20, $p < 0.05$ and E10 + S40, $p < 0.001$); HDL-C (only E10 + S20, $p < 0.05$). <p>Safety: ezetimibe + simvastatin > simvastatin</p> <ul style="list-style-type: none"> • More patients in the ezetimibe + simvastatin groups experienced adverse events that were considered possibly, probably, or definitely related to study-treatment; however, the differences did

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	<p>mg/dl</p> <ul style="list-style-type: none"> • TG \leq350 mg/dl • Liver transaminase and creatine kinase \leq50% above the ULN 	<p>not appear to be driven by any specific event.</p> <ul style="list-style-type: none"> • There were no cases of rhabdomyolysis during the study. Three patients (two S20 and one E10 + S40) had creatine kinase elevations \geq10 times ULN. The two monotherapy cases were considered exercise-related. The co-administration case also had muscle symptoms and was considered possibly related to treatment. • There were no reports of hepatitis or other clinical hepatotoxicity. Two patients (one E10 + S10, one E10 + S40) had consecutive elevations \geq3 times ULN for ALT and/or AST. Both cases were considered possibly treatment-related, but the elevations were transient and asymptomatic.
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ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the curve; AWP = average wholesale price; C_{max} = maximum plasma concentration; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NCEP ATP = National Cholesterol Education Program Adult Treatment Panel; TC = total cholesterol; TG = triglycerides; ULN = upper limit of normal; URT = upper respiratory tract

Conclusion:

The combination of ezetimibe with simvastatin results in synergistic cholesterol-lowering effects. When ezetimibe is used in combination with 10 to 80 mg of simvastatin, LDL-C reductions > 51% can be achieved compared to LDL-C reductions of 36 to 40% with simvastatin monotherapy. The adverse effect profile for combined ezetimibe/statin therapy is similar to statin monotherapy, except for an increase in the incidence of hepatic enzyme elevations observed with combined ezetimibe/statin therapy. In July 2004, the FDA approved the combination of ezetimibe/simvastatin (Vytorin[®]) for adjunctive therapy to diet in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia or mixed hyperlipidemia; the drug is also approved for patients with homozygous familial hypercholesterolemia (HoFH). The Vytorin[®] combination product is cost-effective, based on average wholesale costs, compared to taking the individual drugs separately.

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