

VYTORIN™ 10/10
(EZETIMIBE 10 MG/SIMVASTATIN 10 MG TABLETS)

VYTORIN™ 10/20
(EZETIMIBE 10 MG/SIMVASTATIN 20 MG TABLETS)

VYTORIN™ 10/40
(EZETIMIBE 10 MG/SIMVASTATIN 40 MG TABLETS)

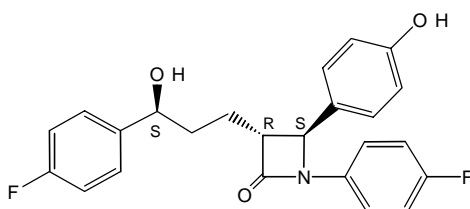
VYTORIN™ 10/80
(EZETIMIBE 10 MG/SIMVASTATIN 80 MG TABLETS)

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.

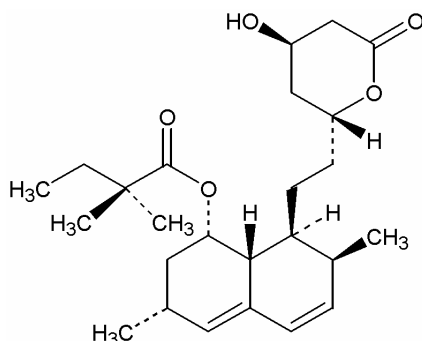
The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$ and its molecular weight is 409.4.

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:



Simvastatin, an inactive lactone, is hydrolyzed to the corresponding β -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-[1 α ,3 α ,7 β ,8 β (2S*,4S*),-8a β]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ 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:



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. 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 and appears to act 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 β -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 ^{14}C -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 β -hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is a basis for an assay in pharmacokinetic studies of the β -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 β -hydroxyacid of simvastatin and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives.

Plasma concentrations of total radioactivity (simvastatin plus ^{14}C -metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be >60% in man), the availability of drug to the general circulation is low.

Following an oral dose of ^{14}C -labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug.

In a single-dose study in nine healthy subjects, it was estimated that less than 5% of an oral dose of simvastatin reaches the general circulation as active inhibitors.

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 (≥ 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 Blacks and Caucasians. There were too few patients in other racial or ethnic groups to permit further pharmacokinetic comparisons.

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 ≤ 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.

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™ 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.

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).

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.

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 study¹, 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 β -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 first¹ 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 β -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 μ 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 μ g/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.

¹ Lilja JJ, Kivisto KT, Neuvonen PJ. Clin Pharmacol Ther 1998;64(5):477-83.

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