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VYTORIN™: ATTACKING CHOLESTEROL WITH A DUAL MECHANISM

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In July 2004, the National Cholesterol Education Panel (NCEP) published an update of the Adult Treatment Panel III (ATP III) cholesterol guidelines that were previously released in 2001. The update, entitled "Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines", endorses more aggressive cholesterol-lowering treatment for people at high and moderately high risk for heart disease. The publication presents data from recent clinical trials, which showed that aggressive lowering of low-density lipoprotein cholesterol (LDL-C) was associated with a reduced risk of suffering from a cardiovascular event. Although it is unclear whether clinical benefit was due to the low level of LDL-C or to non-lipid lowering effects of statins, these results have led to a lowering of the target LDL-C goals to 70 mg/dl or less in "very high risk" patients.[1] The higher the risk, the more aggressively LDL should be treated.

Current statistics show nearly 105 million American adults have total cholesterol (TC) levels greater than 200 mg/dL.[2] This astonishing statistic implies that there are many people in America at increased risk for coronary heart disease (CHD). Reduction in LDL-C is a crucial means for lowering the risk of CHD and subsequent outcomes. There are two main ways to lower cholesterol. First, there is therapeutic lifestyle changes (TLC) which includes a cholesterol-lowering diet, physical activity, and weight management. The second option is through drug treatment. If cholesterol-lowering drugs are needed, they are used together with TLC to help lower LDL. Over the past decade many new cholesterol lowering options have been approved. These include fibric acid derivatives (i.e., fibrates), niacin, bile acid sequestrants (e.g., cholestyramine), hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins), and more recently, cholesterol absorption inhibitors (e.g., ezetimibe).

In July 2004, Merck/Schering-Plough Pharmaceuticals announced that the FDA approved their new combination product, Vytorin™. The new product is a combination of previously approved simvastatin and ezetimibe. Vytorin™ was approved for the treatment of high LDL-C in patients with primary hypercholesterolemia or mixed hyperlipidemia as adjunctive therapy to TLC when TLC alone is not enough. Ezetimibe (Zetia®), the first and only cholesterol absorption inhibitor, was approved by the FDA in October 2003 for the treatment of hypercholesterolemia. The other compo-

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Table 1. LDL cholesterol goal attainment after the first treatment period and at the end of treatment*.[6]

Treatment	S(20)	E(10) + S(10)	E(10) + S(20)	E(10) + S(40)
After First Treatment Period (week 5)	(n=246)	(n=242)	(n=108)	(n=96)
No. (%) of patients attaining LDL cholesterol goal (<100 mg/dl)	112 (46%)	181 (75%)†	90 (83%)†	84 (87%)†
End of the Study				
No. (%) of patients attaining LDL cholesterol goal (<100 mg/dl)*	147 (59%)	190 (78%)†	90 (83%)†	83 (86%)†
Percentage of patients requiring simvastatin up-titration‡	68	33†	22†	12†

E = ezetimibe (milligrams); S = simvastatin (milligrams). *Modified intention-to-treat population that included patients with baseline and > 1 post-baseline measurement during treatment period. †p<0.001 versus S20. ‡Based on entire study cohort regardless of whether patients were at goal at the end of the study.

nent, simvastatin, was approved by the FDA in December 1991 under the brand name Zocor ® for the treatment of hypercholesterolemia. This article will review the pharmacology, clinical trials, and pertinent prescribing information for Vytorin™.

Pharmacology and Pharmacokinetics

Vytorin™ contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action.[3-5] Vytorin™ reduces elevated TC, LDL-C, apolipoprotein B (Apo B), triglycerides (TG), and non-high density lipoprotein cholesterol (non-HDL-C), and increases HDL-C through dual inhibition of cholesterol absorption and synthesis.

Ezetimibe has a mechanism unlike any other cholesterol lowering compound. Ezetimibe decreases LDL-C by inhibiting the absorption of cholesterol by the small intestine. It does not inhibit cholesterol synthesis in the liver like statins, nor does it increase bile acid secretion like bile acid sequestrants. Ezetimibe localizes and acts on the brush border of the small intestine inhibiting cholesterol absorption. This leads to a decrease in delivery of intestinal cholesterol to the liver. The decrease in cholesterol delivery to the liver causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe has no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E and does not impair adrenocortical steroid hormone production. This unique mechanism of action is complementary to that of statins.

Simvastatin is a specific inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol. Simvastatin reduces both normal and elevated LDL-C concentrations. In addition, simvastatin reduces very low density lipoproteins (VLDL) and TG, and minimally increases HDL-C.

Specific pharmacokinetic drug interaction studies with Vytorin™ have not been performed. No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with simvastatin. Ezetimibe administered alone had no significant effect on the cytochrome P450 enzyme system. Tests indicate that ezetimibe is neither an inhibitor nor an inducer of the CYP450 isozymes, and is unlikely to affect the metabolism of drugs that are metabolized by these enzymes.

Simvastatin is a substrate of the CYP450 isoform 3A4. It does not inhibit CYP3A4; therefore, it is not expected to affect the plasma levels of other drugs metabolized by these enzymes. Potent inhibitors of CYP3A4 can raise plasma levels of some statin drugs (e.g., simvastatin, atorvastatin, lovastatin), thereby increasing the risk of myopathy. Patients using drugs that inhibit CYP3A4 should be monitored more closely for statin-related adverse effects. This includes grapefruit juice, which inhibits CYP3A4 in the gut wall, thus, increasing statin exposure.

Following oral administration of a 10 mg dose of ezetimibe, a C_{max} of 3.4 – 5.5 ng/ml was reached within 4 to 12 hours. The C_{max} value of ezetimibe was increased by 38% with consumption of high fats meals. However, concomitant food administra-

Table 2. Percentage change in lipid parameters after the first treatment period.[6]

	Least Square Mean (SE) % Change From Baseline After First Treatment Period (5 weeks)			
Treatment	**S(20)**	**E(10) + S(10)**	**E(10) + S(20)**	**E(10) + S(40)**
	(n=248)	(n=245)	(n=109)	(n=97)
LDL cholesterol	-38 (0.8)	-47 (0.8) *	-53 (1.2) *	-59 (1.3) *
Total Cholesterol	-27 (0.7)	-33 (0.6) *	-38 (0.9) *	-42 (1.0) *
Non-HDL-C	-34 (0.8)	-42 (0.8) *	-48 (1.1) *	-53 (1.2) *
Triglyceride	-19 (1.9)	-19 (1.5)	-25 (2.7) *	-30 (2.6) *
HDL cholesterol	5.1 (0.7)	6.2 (0.7)	8.0 (1.0)*	7.4 (1.1)
LDL-C: HDL-C	-41 (0.8)	-50 (0.8) *	-56 (1.2) *	-61 (1.3) *

SE denotes standard error. E = ezetimibe (milligrams); S = simvastatin (milligrams). * $p<0.001$ versus S20.

tion (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe. Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Both the parent compound and its active metabolite are slowly eliminated from the plasma with a half-life of approximately 22 hours.

Absorption of simvastatin is 85%, but bioavailability is less than 5% due to a significant first pass effect. Food had no effect on the rate and extent of absorption. Simvastatin is administered as an inactive prodrug and must be activated in the liver. Sixty percent of an oral dose is excreted in the feces and 13% in the urine. The half-life of simvastatin is 1.9 hours. Simvastatin circulates in plasma highly bound to plasma proteins (>95%), predominantly albumin.

Dosage and Administration

Vytorin™ is available as tablets containing 10 mg of ezetimibe combined with 10, 20, 40 or 80 mg of simvastatin. The dosage should be individualized according to the baseline LDL-C level, the recommended goal of therapy (NCEP ATP III Guidelines), and patient response. The recommended starting dose is 10/20 mg/day.[3] Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL-C reduction. Patients who require a larger reduction in LDL-C (greater than 55%) may be started at 10/40 mg/day.[3] No dosage adjustment is needed for mild hepatic impairment. Active liver disease is a contraindication for simvastatin use. Avoid Vytorin™ in patients with moderate to severe hepatic impairment or any persistent and unexplained increases in LFTs.[5] No dosage adjustment is necessary in patients with mild or moderate renal impairment. In patients with a CrCl $\leq$ 30 ml/min, do not start Vytorin™ unless the patient has already tolerated monotherapy with simvastatin $\geq$ 5 mg/day.[1] Vytorin™ should be taken as a single dose in the evening, with or without food.

Clinical Trials

In a 23 week, multi-center, parallel group study, 710 patients with LDL-C $\geq$130 mg/dl with CHD or an equivalent were randomized to 1 of 4 treatment groups.[6] Patients received simvastatin 20 mg, ezetimibe 10 mg plus simvastatin 10 mg, ezetimibe 10 mg plus simvastatin 20 mg, or ezetimibe 10 mg plus simvastatin 40 mg. Simvastatin was titrated up every 6 weeks to a maximal dose of 80 mg in patients who did not achieve target LDL-C goal. The primary objective was to evaluate the efficacy of ezetimibe 10 mg plus simvastatin 10 mg versus simvastatin 20 mg monotherapy in attaining the target LDL-C goal of <100 mg/dl after 5 weeks. Secondary endpoints included the percentage of patients achieving goal at study close, the number of simvastatin dose titrations, and the median simvastatin dose used throughout the study.

The percentage of patients achieving the LDL-C goal of <100 mg/dl after the first treatment period (week 5) in the ezetimibe plus simvastatin 10, 20, and 40 mg groups (75%, 83%, and 87% respectively) was significantly greater than in the simvas-

Table 3. Response to Vytorin™ and atorvastatin in patients with primary hypercholesterolemia.[7]

		Mean % Change from Untreated Baseline[a]				
Treatment	**N**	**Total-C**	**LDL-C**	**HDL-C**	**Tg[b]**	**Non-HDL-C**
Week 6						
Atorvastatin 10 mg[c]	262	-28	-37	+5	-23	-35
Vytorin™ 10/10[d]	263	-34[f]	-46[f]	+8[f]	-26	-43[f]
Vytorin™ 10/20[e]	263	-36[f]	-50[f]	+10[f]	-25	-46[f]
Week 12						
Atorvastatin 20 mg	246	-33	-44	+7	-28	-42
Vytorin™ 10/20	250	-37[f]	-50[f]	+9	-28	-46[f]
Vytorin™ 10/40	252	-39[f]	-54[f]	+12[f]	-31	-50[f]
Week 18						
Atorvastatin 40 mg	237	-37	-49	+8	-31	-47
Vytorin™ 10/40[g]	482	-40[f]	-56[f]	+11[f]	-32	-52[f]
Week 24						
Atorvastatin 80 mg	228	-40	-53	+6	-35	-50
Vytorin™ 10/80[g]	459	-43[f]	-59[f]	+12[f]	-35	-55[f]

[A] Baseline – on no lipid-lowering drug. [B] For triglycerides, median % change from baseline. [c] Atorvastatin: 10 mg start dose titrated to 20, 40, and 80 mg through weeks 6, 12, 18, and 24. [d]Vytorin™:start 10/10 start dose titrated to 10/20, 10/40, and 10/80 through weeks 6, 12, 18, and 24. [e]Vytorin™:start 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.

tatin 20 mg group (46%; $p<0.001$ for all 3 comparisons; Table 1). Patients treated with ezetimibe 10 mg plus simvastatin 10 mg had a 3.6 fold greater risk of reaching goal after 5 weeks than patients treated with simvastatin 20 mg (odds ratio [OR], 3.6; 95% CI, 2.4 to 5.2). The data in Table 2 show that mean plasma levels of LDL-C were reduced significantly more by all doses of ezetimibe plus simvastatin than by simvastatin 20 mg after the first treatment period. Relative to simvastatin 20 mg, ezetimibe plus simvastatin 10 mg also produced significantly larger reductions in TC, non-HDL, and the ratio of LDL-C to HDL-C. Triglycerides were significantly reduced by ezetimibe plus simvastatin 20 and 40 mg compared with simvastatin 20 mg. Although HDL-C was numerically greater in all 3 co-administration groups than in the simvastatin 20 mg group, the increase was only significant in the ezetimibe plus simvastatin 20 mg arm.

In a 28-week (4 week placebo/diet run in and 24 week active treatment period) multi-center, active-controlled, double blind study, 788 patients with an LDL-C level at or above drug treatment threshold established by NCEP ATP III guidelines were randomized to receive co-administered ezetimibe and simvastatin (equivalent to Vytorin™ 10/10 and 10/20) or atorvastatin 10 mg.[7] For all three treatment groups, the dose of the statin was titrated at 6 week intervals to 80 mg. The primary efficacy measure was mean percentage change in LDL-C from baseline to the end of the initial 6-week treatment period. Key secondary efficacy measures included percent change from baseline to the end of the second and fourth (final) 6-week treatment periods and percentage change in HDL-C from baseline to the end of the final 6-week treatment period. Table 3 depicts the mean percentage change from baseline measured at each 6 week interval. At each pre-specified dose comparison, co-administered ezetimibe and simvastatin significantly lowered total cholesterol and LDL-C to a greater degree than atorvastatin. At 24 weeks, mean change in HDL-C levels for patients taking 10 mg ezetimibe plus 80 mg of simvastatin were also significantly greater than for patients treated with atorvastatin 80 mg. (Table 3)

Table 4. Clinical Adverse Events* Occurring in ≥2% of Patients Treated with Vytorin™.[3]

Body System/Organ Class	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
Infections 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 co-administered and one placebo-controlled study in which Vytorin™ was administered. Adverse events are reported regardless of causality. **All doses.

Precautions and Warnings/Contraindications

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone).[3] However, myopathy and rhabdomyolysis are known to occur in patients treated with statins and other lipid lowering agents and, thus, may occur with Vytorin™. In clinical trials, the incidence of creatinine kinase (CK) >10 times the upper limit of normal was 0.2% for Vytorin™. Increases in serum transaminases (3 times above normal) occurs slightly more often with the combination of ezetimibe and a statin than with a statin alone (1.3% vs. 0.4%).

Vytorin™ is pregnancy category X and should not be used in pregnant women and administered to women of childbearing age only when such patients are highly unlikely to conceive. Cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. HMG-CoA reductase inhibitors, such as simvastatin, block the cholesterol biosynthesis pathway increasing the potential risks to the fetus. If the patient becomes pregnant while taking this drug, it should be discontinued immediately. Patients that have active liver disease or unexplained persistent elevations in serum transaminases or have hypersensitivity to any component of this medication should not use Vytorin™.

Adverse Reactions

Vytorin™ has been evaluated for safety in more than 3800 patients in clinical trials.[3] Vytorin™ was generally well tolerated. Table 4 summarizes adverse events reported in ≥2% of patients treated with Vytorin™ (n=1236) and at incidence greater than placebo regardless of causality from three similarly designed, placebo-controlled trials. Other adverse reactions that have been reported include abdominal pain, nausea, diarrhea; hypersensitivity reactions, including angioedema and rash; pancreatitis; cholelithiasis; cholecystitis.

Drug Interactions

Vytorin™ should be used cautiously with known inhibitors of the CYP3A4 enzymes.[3,5] Concomitant use of CP3A4 inhibitors increases the risk for myopathy/rhabdomyolysis by reducing the elimination of the simvastatin component. When administering Vytorin™ with amiodarone or verapamil, the dose should not exceed 10/20 mg daily. Caution should also be exercised when initiating Vytorin™ in patients treated with cyclosporine due to increased exposure to ezetimibe. The dose should not exceed 10/10 mg daily in patients receiving cyclosporine.

Vytorin™ should not be administered with other statins. Since compounds in red yeast rice are chemically similar to lovastatin, red yeast rice should not be used in combination with statins. Concomitant use can increase the risk of drug-related toxicity, such as myopathy, rhabdomyolysis, and/or transaminitis.

Co-administration of Vytorin™ with fibrates is not recommended until clinical trials have been

Table 5. Average cost* of Vytorin ™ and its components

Drug	Tablet Size	Cost*
Vytorin™	10/10 mg	$84.24
	10/20 mg	$84.24
	10/40 mg	$84.24
	10/80 mg	$84.24
Ezetimibe (Zetia®)	10 mg	$77.77
Simvastatin (Zocor®)	10 mg	$79.02
	20 mg	$137.87
	40 mg	$137.87
	80 mg	$137.87

*Cost information derived from reference 1.

conducted to establish safety and efficacy. In a pharmacokinetic study, concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations by approximately 1.5 or 1.7-fold, respectively. The combined use of ezetimibe with fibrates has not been thoroughly studied and should be used with caution if at all.

Vytorin™ is expected to interact with the bile acid sequestrants. The oral absorption of ezetimibe is decreased by the concomitant administration of cholestyramine, resulting in reduced efficacy of ezetimibe. A similar effect might be expected to occur with co-administration of colestipol. No data are available for colesevelam, a bile acid sequestrant that exhibits few absorptive interactions. To limit interactions, dosing of Vytorin™ should occur either $\geq$ 2 hours before or $\geq$ 4 hours after administration of a bile acid sequestrant.

Cost

The cost of a 30-day supply of Vytorin™ and its separate components are depicted in Table 5.[1]

Summary

Vytorin™ is the newest addition to the cholesterol lowering drug market. It offers substantial cholesterol lowering power through a combination of two separate medications, simvastatin and ezetimibe, with two distinct mechanisms. The fixed dose combination of ezetimibe and simvastatin is more convenient and less expensive than taking the 2 drugs separately. Since clinical outcomes data is still unavailable Vytorin™ should not be considered as a first line lipid-lowering agent. Vytorin™ should be considered as a viable option for patients in which high dose statins are contraindicated or intolerable and intense lipid lowering therapy is needed. The combination of ezetimibe and simvastatin offers high-risk patients the opportunity to reach LDL-C goals in accordance with the newly updated ATP III guidelines when a statin alone has been insufficient or higher doses can not be tolerated. Vytorin™ offers a well-tolerated, efficacious treatment strategy for patients with hypercholesterolemia.

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