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LOCAL PRODUCT CIRCULAR

Tablets

VYTORIN® 10/10
(EZETIMIBE 10 MG/SIMVASTATIN 10 MG)
VYTORIN® 10/20
(EZETIMIBE 10 MG/SIMVASTATIN 20 MG)
VYTORIN® 10/40
(EZETIMIBE 10 MG/SIMVASTATIN 40 MG)

I. THERAPEUTIC CLASS

VYTORIN (ezetimibe/simvastatin) is a lipid-lowering product that selectively inhibits the intestinal absorption of cholesterol and related plant sterols and inhibits the endogenous synthesis of cholesterol.

II. COMPOSITION

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) or 40 mg of simvastatin (VYTORIN 10/40).

III. CLINICAL PHARMACOLOGY

IIIa. Mechanism 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 inhibits the intestinal absorption of cholesterol. Ezetimibe is orally active and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g., statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction.

In a 2-week clinical study in 18 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo.

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

Simvastatin
After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed in the liver to the corresponding active β-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy - 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases HDL-C and reduces plasma TG. As a result of these changes, the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

IIIb. Pharmacokinetics

IIIb-1. Absorption

Ezetimibe
After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10-mg tablets.

Simvastatin
The availability of the β-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose, consistent with extensive hepatic first-pass extraction. The major metabolites of simvastatin present in human plasma are the β- hydroxyacid and four additional active metabolites.

Relative to the fasting state, the plasma profiles of both active and total inhibitors were not affected when simvastatin was administered immediately before a test meal.

IIIb-2. Distribution

Ezetimibe
Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.
Simvastatin
Both simvastatin and the β-hydroxyacid are bound to human plasma proteins (95%).

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of drug occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1.3 to 2.4 hours post-dose.

IIIb-3. Metabolism

Ezetimibe

Ezetimibe is metabolized primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. 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 evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Simvastatin

Simvastatin is an inactive lactone which is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

In man simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is its primary site of action, with subsequent excretion of drug equivalents in the bile. Consequently, availability of active drug to the systemic circulation is low.

Following an intravenous injection of the β-hydroxyacid metabolite, its half-life averaged 1.9 hours.

IIIb-4. Elimination

Ezetimibe

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Simvastatin

Following an oral dose of radioactive simvastatin to man, 13% of the radioactivity was excreted in the urine and 60% in the feces within 96 hours. The amount recovered in the feces represents absorbed drug equivalents excreted in bile as well as unabsorbed drug. Following an intravenous injection of the β-hydroxyacid metabolite an average of only 0.3% of the IV dose was excreted in urine as inhibitors.

IIIb-5. Characteristics in Patients (Special Populations)

Pediatric Patients

The absorption and metabolism of ezetimibe are similar between children and 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.

Geriatric Patients

Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable betweenelderly and young subjects treated with ezetimibe.

Hepatic Insufficiency

After a single 10-mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score >9) hepatic insufficiency, ezetimibe is not recommended in these patients (see VIII. PRECAUTIONS).

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 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9).

An additional patient in this study (post-renal transplant and receiving multiple medications,including cyclosporine) had a 12-fold greater exposure to total ezetimibe.

Simvastatin

In a study of patients with severe renal insufficiency (creatinine clearance <30 mL/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately two-fold higher than those in healthy volunteers.

Gender

Plasma concentrations for total ezetimibe are slightly higher (<20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe.

Race

Based on a meta-analysis of pharmacokinetic studies with ezetimibe, there were no pharmacokinetic differences between Blacks and Caucasians.

IIIb-6. Drug Interactions

Diltiazem

In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase inexposure of simvastatin acid, presumably due to inhibition of CYP3A4.

Amlodipine

In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid.

IV. INDICATIONS

Prevention of Cardiovascular Events
VYTORIN is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, or need for revascularization), in patients with coronary heart disease (CHD) and history of acute coronary syndrome (ACS), either previously treated with a statin or not.

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

Homozygous Familial Hypercholesterolemia (HoFH)
VYTORIN is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

V. DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving VYTORIN and should continue on this diet during treatment with VYTORIN. The dosage should be individualized according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response. VYTORIN should be taken as a single daily dose in the evening, with or without food.

Patients with Primary Hypercholesterolemia
In patients with primary hyperlipidemia or mixed hyperlipidemia, the dosage range is 10/10 mg/day through 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL-C reductions. Patients who require a larger reduction in LDL-C (greater than 55%) may be started at 10/40 mg/day. After initiation or titration of VYTORIN, lipid levels may be analyzed after 2 or more weeks and dosage adjusted, if needed. The 10/80 mg dose of VYTORIN is only recommended in patients at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks (see VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

For patients who are currently on both simvastatin and ezetimibe, no dosage adjustment is required when switching to VYTORIN.

Patients with Coronary Heart Disease
In the cardiovascular events risk reduction study (IMPROVE-IT), the starting dose was 10/40 mg once a day in the evening. The 10/80-mg dose is only recommended when the benefits are expected to outweigh the potential risks. (See VIII. PRECAUTIONS *and VI. Clinical Studies.*)

Patients with Homozygous Familial Hypercholesterolemia
The recommended dosage for patients with homozygous familial hypercholesterolemia is VYTORIN 10/40 mg/day or 10/80 mg/day in the evening. The 10/80-mg dose is only recommended when the benefits are expected to outweigh the potential risks (see above, VII. CONTRAINDICATIONS, and VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

VYTORIN should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

In patients taking lomitapide concomitantly with VYTORIN, the dose of VYTORIN should not exceed 10/40 mg/day (see VIII. PRECAUTIONS, Myopathy/Rhabdomyolysis and XII. DRUG INTERACTIONS).

Use in the Elderly
No dosage adjustment is required for elderly patients (see *IIIb-5. Characteristics in Patients [Special Populations]*).

Use in Pediatric Patients
Treatment with VYTORIN is not recommended.

Use in Hepatic Impairment
No dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6). Treatment with VYTORIN is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score > 9) liver dysfunction (see VIII. PRECAUTIONS and *IIIb-5. Characteristics in Patients [Special Populations]*).

Use in Renal Impairment
No dosage adjustment is required for patients with moderate renal insufficiency. If treatment in patients with severe renal insufficiency (creatinine clearance ≤ 30 mL/min) is deemed necessary, dosages above 10/10 mg/day should be implemented cautiously (see *IIIb-5. Characteristics in Patients [Special Populations]*).

Coadministration with other medicines
Dosing of VYTORIN should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.

In patients taking amiodarone, verapamil, diltiazem, or products containing elbasvir or grazoprevir concomitantly with VYTORIN, the dose of VYTORIN should not exceed 10/20 mg/day (see VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis* and XII. DRUG INTERACTIONS).

In patients taking amlodipine concomitantly with VYTORIN, the dose of VYTORIN should not exceed 10/40 mg/day (see VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis* and XII. DRUG INTERACTIONS).

The safety and effectiveness of VYTORIN administered with fibrates have not been studied. Therefore, the combination of VYTORIN and fibrates should be avoided (see VII. CONTRAINDICATIONS, VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis* and XII. DRUG INTERACTIONS).

VI. CLINICAL STUDIES

In controlled clinical studies, VYTORIN significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non- high-density lipoprotein cholesterol (non-HDL-C), and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolemia.

VYTORIN
Prevention of Cardiovascular Disease
The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)

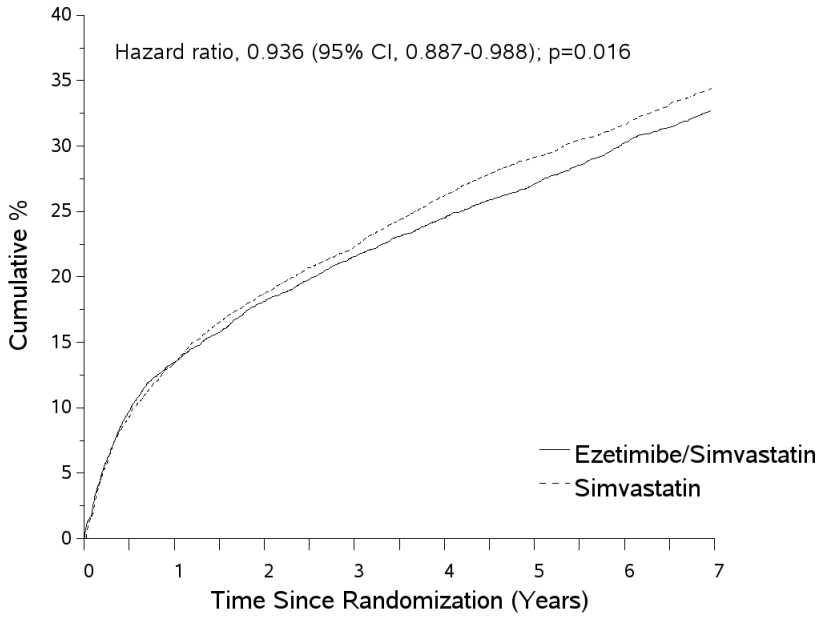
was a multicenter, randomized, double-blind, active-control study of 18,144 patients enrolled within 10 days of hospitalization for acute coronary syndrome (ACS; either acute myocardial infarction [MI] or unstable angina [UA]). Patients had an LDL-C ≤ 125 mg/dL (≤ 3.2 mmol/L) at the time of presentation with ACS if they had not been taking lipid-lowering therapy, or ≤ 100 mg/dL (≤ 2.6 mmol/L) if they had been receiving lipid-lowering therapy. All patients were randomized in a 1:1 ratio to receive either VYTORIN 10/40 mg (n=9067) or simvastatin 40 mg (n=9077) and followed for a median of 6.0 years.

Patients had a mean age of 63.6 years; 76% were male, 84% were Caucasian, and 27% were diabetic. The average LDL-C value at the time of study qualifying event was 80 mg/dL (2.1 mmol/L) for those on lipid-lowering therapy (n=6390) and 101 mg/dL (2.6 mmol/L) for those not on previous lipid-lowering therapy (n=11594). Prior to the hospitalization for the qualifying ACS event, 34% of the patients were on statin therapy. At one year, the average LDL-C for patients continuing on therapy was 53.2 mg/dL (1.4 mmol/L) for the VYTORIN group and 69.9 mg/dL (1.8 mmol/L) for the simvastatin monotherapy group. Lipid values were generally obtained for patients who remained on study therapy.

The primary endpoint was a composite consisting of cardiovascular death, major coronary events (MCE; defined as non-fatal myocardial infarction, documented unstable angina that required hospitalization, or any coronary revascularization procedure occurring at least 30 days after randomized treatment assignment) and non-fatal stroke. The study demonstrated that treatment with VYTORIN provided incremental benefit in reducing the primary composite endpoint of cardiovascular death, MCE, and non-fatal stroke compared with simvastatin alone (relative risk reduction of 6.4%, p=0.016). The primary endpoint occurred in 2572 of 9067patients (7-year Kaplan-Meier [KM] rate 32.72%) in the VYTORIN group and 2742 of 9077 patients (7-year KM rate 34.67%) in the simvastatin alone group. (See Figure 1 and Table 1.)

The treatment effect of VYTORIN was generally consistent with the overall results across many subgroups, including sex, age, race, medical history of diabetes mellitus, baseline lipid levels, prior statin therapy, prior stroke, and hypertension (see Figure 2).

Figure 1: Effect of VYTORIN on the Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke



Subjects at risk								
Ezetimibe/Simvastatin	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

Figure 2: Subgroup Analysis of Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke

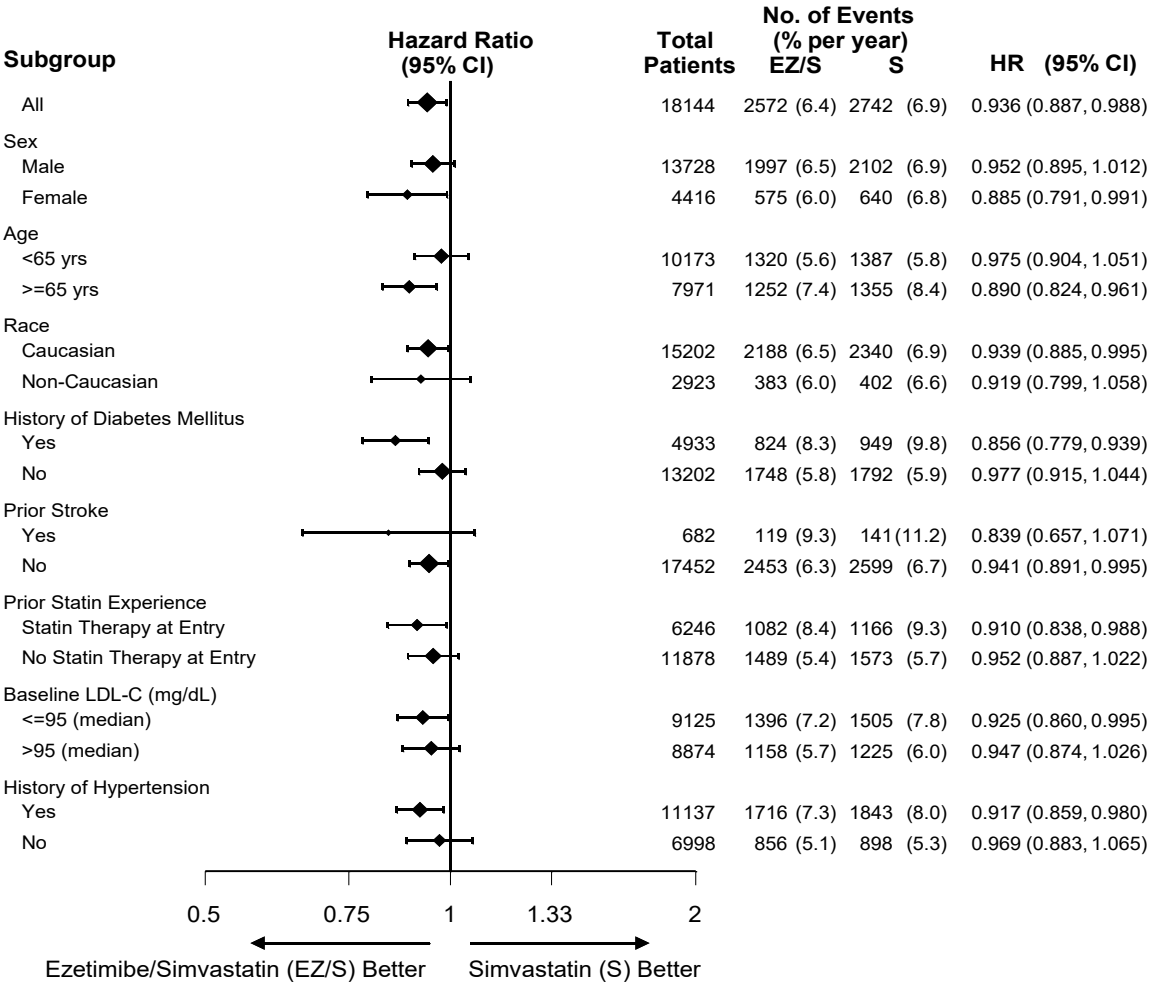


Table 1
Major Cardiovascular Events by Treatment Group in All Randomized Patients in IMPROVE-IT

Outcome	VYTORIN 10/40 mg* (N=9067)		Simvastatin 40 mg† (N=9077)		Hazard Ratio (95% CI)	p-value
	n	K-M %‡	n	K-M %‡		
Primary Composite Efficacy Endpoint						
(CV death, Major Coronary Events and non-fatal stroke)	2572	32.72%	2742	34.67%	0.936 (0.887, 0.988)	0.016
Secondary Composite Efficacy Endpoints						
CHD death, nonfatal MI, urgent coronary revascularization after 30 days	1322	17.52%	1448	18.88%	0.912 (0.847, 0.983)	0.016
MCE, non-fatal stroke, death (all causes)	3089	38.65%	3246	40.25%	0.948 (0.903, 0.996)	0.035
CV death, non-fatal MI, unstable angina requiring hospitalization, any revascularization, non-fatal stroke	2716	34.49%	2869	36.20%	0.945 (0.897, 0.996)	0.035
Components of Primary Composite Endpoint and Select Efficacy Endpoints (first occurrences of specified event at any time)						
Cardiovascular death	537	6.89%	538	6.84%	1.000 (0.887, 1.127)	0.997
Major Coronary Event:						
Non-fatal MI	945	12.77%	1083	14.41%	0.871 (0.798, 0.950)	0.002
Unstable angina requiring hospitalization	156	2.06%	148	1.92%	1.059 (0.846, 1.326)	0.618
Coronary revascularization after 30 days	1690	21.84%	1793	23.36%	0.947 (0.886, 1.012)	0.107
Non-fatal stroke	245	3.49%	305	4.24%	0.802 (0.678, 0.949)	0.010
All MI (fatal and non-fatal)	977	13.13%	1118	14.82%	0.872 (0.800, 0.950)	0.002
All stroke (fatal and non-fatal)	296	4.16%	345	4.77%	0.857 (0.734, 1.001)	0.052
Non-hemorrhagic stroke§	242	3.48%	305	4.23%	0.793 (0.670, 0.939)	0.007
Hemorrhagic stroke	59	0.77%	43	0.59%	1.377 (0.930, 2.040)	0.110
Death from any cause	1215	15.36%	1231	15.28%	0.989 (0.914, 1.070)	0.782

* 6% were uptitrated to ezetimibe/simvastatin 10/80 mg.
† 27% were uptitrated to simvastatin 80 mg.
‡ Kaplan-Meier estimate at 7 years.
§ includes ischemic stroke or stroke of undetermined type.

Primary Hypercholesterolemia
VYTORIN

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

In a multicenter, double-blind, placebo-controlled, 12-week trial, 887 hypercholesterolemic patients were randomized to one of ten treatment groups: placebo, ezetimibe (10 mg), simvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/10, 10/20, 10/40, and 10/80). When patients receiving VYTORINwere compared to those receiving all doses of simvastatin, VYTORIN significantly lowered total- C, LDL-C, Apo B, TG, non-HDL-C, and C-reactive protein. The effects of VYTORIN on HDL-C were similar to the effects seen with simvastatin. Further analysis showed VYTORIN significantly increased HDL-C compared with placebo. (see Table 2)

Table 2
Response to VYTORIN in Patients with Primary Hypercholesterolemia
(Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG[a]	Non-HDL-C
Pooled data (All VYTORIN doses)[c]	353	-38	-53	-42	+8	-28	-49
Pooled data (All simvastatin doses)[c]	349	-26	-38	-29	+8	-15	-34
Ezetimibe 10 mg	92	-14	-20	-15	+7	-13	-19
Placebo	93	+2	+3	+3	+2	-2	+2
VYTORIN by dose							
10/10	87	-32	-46	-36	+9	-21	-41
10/20	86	-37	-51	-41	+8	-31	-47
10/40	89	-39	-55	-44	+9	-32	-51
10/80	91	-43	-61	-47	+6	-28	-55
Simvastatin by dose							
10 mg	81	-21	-31	-23	+5	-4	-27
20 mg	90	-24	-35	-25	+6	-14	-31
40 mg	91	-29	-42	-33	+8	-19	-37
80 mg	87	-32	-46	-35	+11	-26	-41

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] VYTORIN doses pooled (10/10-10/80) significantly reduced total-C, LDL-C, Apo B, TG, and non-HDL-C compared to simvastatin, and significantly increased HDL-C compared to placebo.

In a similarly designed study, results for all lipid parameters were generally consistent. In a pooled analysis of these two studies, the lipid response to VYTORIN was similar in patients with TG levels greater than or less than 200 mg/dL.

In a multicenter, double-blind, controlled, 23-week study, 710 patients with known CHD or CHD risk equivalents, as defined by the NCEP ATP III guidelines, and an LDL-C ≥ 130 mg/dL were randomized to one of four treatment groups: coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/10, 10/20, and 10/40), or simvastatin 20 mg. Patients not reaching an LDL-C <100 mg/dL had their simvastatin dose titrated at 6-week intervals to a maximal dose of 80 mg. At Week 5, the LDL-C reductions with VYTORIN 10/10, 10/20, or 10/40 were significantly larger than with simvastatin 20 mg. In addition, at Week 5, significantly more patients receiving VYTORIN 10/10, 10/20, or 10/40 attained LDL-C target compared to those receiving simvastatin 20 mg (see Table 3). Week 5 results for LDL-C reduction and percentage attaining LDL-C target were consistent with the end of study results (Week 23).

Table 3
Response to VYTORIN after 5 Weeks in Patients with CHD or CHD Risk Equivalentsand an LDL-C ≥ 130 mg/dL

	Simvastatin 20 mg	VYTORIN 10/10	VYTORIN 10/20	VYTORIN 10/40
N	253	251	109	97
Percent change LDL-C	-38	-47	-53	-59
Percent attaining LDL-C goal	46	75	83	88

In a multicenter, double-blind, 6-week study, 1902 patients with primary hypercholesterolemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to one of eight treatment groups: VYTORIN (10/10, 10/20, 10/40, or 10/80) or atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg). When patients receiving all doses of VYTORIN were compared to those receiving all doses of atorvastatin, VYTORIN lowered total-C, LDL-C, Apo B, and non-HDL-C, and increased HDL-C significantly more than atorvastatin. The effects of VYTORIN on TG were similar to the effects seen with atorvastatin. (see Table 4.)

Table 4
Response to VYTORIN and Atorvastatin in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG[a]	Non-HDL-C
Pooled data (All VYTORIN doses)	951	-38[c]	-53[c]	-43[c]	+8[c]	-27	-49[c]
Pooled data (All Atorvastatin doses)	951	-34	-45	-38	+4	-26	-42
VYTORIN by dose							
10/10	238	-34[d]	-47[d]	-37[d]	+8	-26	-43[d]
10/20	238	-37[d]	-51[d]	-40[d]	+7	-25	-46[d]
10/40	238	-41[d]	-57[d]	-46[d]	+9[d]	-27	-52[d]
10/80	237	-43[d]	-59[d]	-48[d]	+8[d]	-31	-54[d]
Atorvastatin by dose							
10 mg	238	-27	-36	-31	+7	-21	-34
20 mg	237	-32	-44	-37	+5	-25	-41
40 mg	237	-36	-48	-40	+4	-24	-45
80 mg	239	-40	-53	-44	+1	-32	-50

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] p<0.05 for difference with atorvastatin
[d] p<0.05 for difference with atorvastatin at equal mg doses of the simvastatin component

In a multicenter, double-blind, 24-week, forced titration study, 788 patients with primary hypercholesterolemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to receive coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/10 and 10/20) or atorvastatin 10 mg. For all three treatment groups, the dose of the statin was titrated at 6- week intervals to 80 mg. At each pre-specified dose comparison, VYTORIN lowered LDL-C to a greater degree than atorvastatin (see Table 5).

Table 5
Response to VYTORIN and Atorvastatin in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment	N	Total-C	LDL-C	Apo B	HDL-C	TG[a]	Non-HDL-C
Week 6							
Atorvastatin 10 mg[c]	262	-28	-37	-32	+5	-23	-35
VYTORIN 10/10[d]	263	-34[f]	-46[f]	-38[f]	+8[f]	-26	-43[f]
VYTORIN 10/20[e]	263	-36[f]	-50[f]	-41[f]	+10[f]	-25	-46[f]
Week 12							
Atorvastatin 20 mg	246	-33	-44	-38	+7	-28	-42
VYTORIN 10/20	250	-37[f]	-50[f]	-41[f]	+9	-28	-46[f]
VYTORIN 10/40	252	-39[f]	-54[f]	-45[f]	+12[f]	-31	-50[f]
Week 18							
Atorvastatin 40 mg	237	-37	-49	-42	+8	-31	-47
VYTORIN 10/40[g]	482	-40[f]	-56[f]	-45[f]	+11[f]	-32	-52[f]
Week 24							
Atorvastatin 80 mg	228	-40	-53	-45	+6	-35	-50
VYTORIN 10/80[g]	459	-43[f]	-59[f]	-49[f]	+12[f]	-35	-55[f]

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

In a multicenter, double-blind, 6-week study, 2959 patients with primary hypercholesterolemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to one of six treatment groups: VYTORIN (10/20, 10/40, or 10/80) or rosuvastatin (10 mg, 20 mg, or 40 mg). When patients receiving all doses of VYTORIN were compared to those receiving all doses of rosuvastatin, VYTORIN lowered total-C, LDL-C, Apo B, TG, and non-HDL-C significantly more than rosuvastatin. The effects of VYTORIN on HDL-C were similar to the effects seen with rosuvastatin (see Table 6).

Table 6
Response to VYTORIN and Rosuvastatin in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG[a]	Non-HDL-C
Pooled data (All VYTORIN doses)	1478	-40[c]	-56[c]	-45[c]	+8	-26[c]	-51[c]
Pooled data (All rosuvastatin doses)	1481	-37	-52	-42	+8	-25	-47
VYTORIN by dose							
10/20	492	-37[d]	-52[d]	-42[d]	+7	-23[d]	-47[d]
10/40	493	-39[e]	-55[e]	-44[e]	+8	-27	-50[e]
10/80	493	-44[f]	-61[f]	-50[f]	+8	-30[f]	-56[f]
Rosuvastatin by dose							
10 mg	492	-32	-46	-37	+7	-20	-42
20 mg	495	-37	-52	-43	+8	-26	-48
40 mg	494	-41	-57	-47	+8	-28	-52

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] p<0.05 for difference with rosuvastatin
[d] p<0.05 vs. rosuvastatin 10 mg
[e] p<0.05 vs. rosuvastatin 20 mg
[f] p<0.05 vs. rosuvastatin 40 mg

In a double-blind, placebo-controlled, 8-week study, 240 patients with hypercholesterolemia already receiving simvastatin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.6 to 4.1 mmol/L [100 to 160 mg/dL], depending on baseline characteristics) were randomized to receive either ezetimibe 10 mg or placebo in addition to their on-going simvastatin therapy. Among simvastatin-treated patients not at LDL-C goal at baseline (~80%), significantly more patients randomized to ezetimibe coadministered with simvastatin achieved their LDL-C goal at study endpoint compared to patients randomized to placebo coadministered with simvastatin, 76% and 21.5%, respectively. The corresponding LDL-C reductions for ezetimibe or placebo coadministered with simvastatin were also significantly different (27% or 3%, respectively). In addition, ezetimibe coadministered with simvastatin significantly decreased total-C, Apo B, and TG compared with placebo coadministered with simvastatin.

In a multicenter, double-blind, 24-week trial, 214 patients with type 2 diabetes mellitus treated with thiazolidinediones (rosiglitazone or pioglitazone) for a minimum of 3 months and simvastatin 20 mg for a minimum of 6 weeks with a mean LDL-C of 93 mg/dL, were randomized to receive either simvastatin 40 mg or the coadministered active ingredients equivalent to VYTORIN 10/20.

VYTORIN 10/20 was significantly more effective than doubling the dose of simvastatin to 40 mg in further reducing LDL-C (-21% and 0%, respectively), total-C (-14% and -1%, respectively), Apo B (-14% and -2%, respectively), and non-HDL-C (-20% and -2%, respectively) beyond the reductions observed with simvastatin 20 mg. Results for HDL-C and TG between the two treatment groups were not significantly different. Results were not affected by type of thiazolidinedione treatment.

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

had no effect on the plasma concentrations of the fat-soluble vitamins A, D, and E, had no effect on prothrombin time, and did not impair adrenocortical steroid hormone production.

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

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

VII. CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and nursing (see IX. PREGNANCY and X. NURSING MOTHERS).
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and drugs containing cobicistat) (see VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis* and XII. DRUG INTERACTIONS).
- Concomitant administration of gemfibrozil, cyclosporine, or danazol (see VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis* and XII. DRUG INTERACTIONS*)*.

VIII. PRECAUTIONS

Myopathy/Rhabdomyolysis
Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The riskof myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma (i.e., elevated simvastatin and simvastatin acid plasma levels), which may be due, in part, to interacting drugs that interfere with simvastatin metabolism and/or transporter pathways (see XI. DRUG INTERACTIONS). Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose

related for simvastatin. In a clinical trial database in which 41,413 patients were treated with simvastatin, 24,747 (approximately 60%) of whom were enrolled in studies with a median follow- up of at least 4 years, the incidence of myopathy was approximately 0.03%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which patients with a history of myocardial infarction were treated with simvastatin 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during eachsubsequent year of treatment was approximately 0.1%.

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C-lowering efficacy. Therefore, the 10/80-mg dose of VYTORINshould only be used in patients at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. In patients taking VYTORIN 10/80 mg for whom an interacting agent is needed, a lower dose of VYTORIN or an alternative statin-ezetimibe regimen with less potential for drug-drug interactions should be used (see below, V. DOSAGE AND ADMINISTRATION, and VII. CONTRAINDICATIONS).

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. The presence of these symptoms, and a CK level >10 times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from simvastatin treatment, muscle symptoms and CK increases resolved (see XIII. SIDE EFFECTS). Periodic CK determinations may be considered in patients starting therapy with VYTORIN or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 10/80 mg dose. 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 whenany major medical or surgical condition supervenes.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) duringor after treatment with some statins. IMNM is clinically characterized by:

- persistent proximal muscle weakness and elevated serum creatine kinase, which persistdespite discontinuation of statin treatment;
- muscle biopsy showing necrotizing myopathy without significant inflammation;
- improvement with immunosuppressive agents.

In the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18,144 patients with CHD were randomized to receive VYTORIN 10/40 mg daily (n=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of myopathy was 0.2% for VYTORIN and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN or two consecutive observations of CK ≥ 5 and <10 times ULN. The incidence of rhabdomyolysis was 0.1% for VYTORIN and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN with evidence of renal injury, ≥ 5 X ULN and <10 X ULN on two consecutive occasions with evidence of renal injury or CK ≥ 10,000 IU/L without evidence of renal injury. (See XIII. SIDE EFFECTS.)

In a clinical trial in which patients at high risk of cardiovascular disease were treated with simvastatin 40 mg/day (median follow-up 3.9 years), the incidence of myopathy was approximately 0.05% for non-Chinese patients (n=7367) compared with 0.24% for Chinese patients (n=5468). While the only Asian population assessed in this clinical trial was Chinese, caution should be used when prescribing VYTORIN to Asian patients and the lowest dose necessary should be employed.

Drug Interactions

- **Because VYTORIN contains simvastatin, the risk of myopathy/rhabdomyolysis is increasedby concomitant use of VYTORIN with the following drugs:**

Contraindicated Drugs

- **Potent inhibitors of CYP3A4:** Concomitant use with medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses **(e.g. itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, or drugs containing cobicistat)** is contraindicated. If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with VYTORIN should be suspended during the course of treatment. (See VII. CONTRAINDICATIONS, XII. DRUG INTERACTIONS; and IIIb. CLINICAL PHARMACOLOGY, Pharmacokinetics.)
- **Gemfibrozil, cyclosporine, or danazol:** Concomitant use of these drugs with VYTORIN is contraindicated (see VII. CONTRAINDICATIONS, XII. DRUG INTERACTIONS, IIIb. CLINICAL PHARMACOLOGY, Pharmacokinetics).

Other Drugs

- **Fusidic acid:** Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy/rhabdomyolysis (see XII. DRUG INTERACTIONS, *Other drug interactions*). Coadministration with fusidic acid is not recommended. In patients where the use of systemic fusidic acid is considered essential, VYTORIN should be discontinued throughout the duration of fusidic acid treatment. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for coadministration of VYTORIN and fusidic acid should only be considered on a case-by-case basis under close medical supervision.

- **Amiodarone:** In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. **The dose of VYTORIN should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone.** (See XII. DRUG INTERACTIONS.)

- **Calcium channel blockers**

  - **Verapamil or diltiazem:** Patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. **The dose of VYTORIN**

should not exceed 10/20 mg daily in patients receiving concomitant medication with verapamil or diltiazem. (See XII DRUG INTERACTIONS, *Other drug interactions*.)

- **Amlodipine:** In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy (see XII. DRUG INTERACTIONS). **The dose of VYTORIN should not exceed 10/40 mg daily in patientsreceiving concomitant medication with amlodipine**

- **Lomitapide: The dose of VYTORIN should not exceed 10/40 mg daily in patients with HoFH receiving concomitant medication with lomitapide (see XII. DRUG INTERACTIONS).**

- **Moderate inhibitors of CYP3A4:** Patients taking other medicines labeled as having a moderate inhibitory effect on CYP3A4 concomitantly with VYTORIN, particularly higher VYTORIN doses, may have an increased risk of myopathy. When coadministering VYTORIN with a moderate inhibitor of CYP3A4, a dose adjustment of VYTORIN may be necessary.

- **Inhibitors of Breast Cancer Resistant Protein (BCRP):** Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore, a dose adjustment of VYTORIN may be necessary. Coadministration of elbasvir and grazoprevir with simvastatin has not been studied; however, **the dose of VYTORIN should not exceed 10/20mg daily in patients receiving concomitant medication with products containing elbasvir or grazoprevir (see. XII DRUG INTERACTIONS, Other drug interactions).**

- **Other Fibrates:** The safety and effectiveness of VYTORIN administered with fibrates, have not been studied. **Therefore, the concomitant use of VYTORIN and fibrates, should be avoided. Concomitant use of gemfibrozil is contraindicated (see VII.CONTRAINDICATIONS).**

- **Niacin (≥1 g/day):** Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day) of niacin. In a clinical trial (median follow-up 3.9 years) involving patients at high risk of cardiovascular disease and with well-controlled LDL-C levels on simvastatin 40 mg/day with or without ezetimibe 10 mg, there was no incremental benefit on cardiovascular outcomes with the addition of lipid-modifying doses (≥ 1 g/day) of niacin. Therefore, the benefit of the combined use of simvastatin with niacin should be carefully weighed against the potential risks of the combination. In addition, in this trial, the incidence of myopathy was approximately 0.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 1.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg coadministered with extended-release niacin/laropiprant 2 g/40 mg. **While the only Asian population assessed in this clinical trial was Chinese, because the incidence of myopathy is higher in Chinese than in non-Chinese patients, coadministration of VYTORIN with lipid-modifying doses (≥ 1 g/day) of niacin is not recommended in Asian patients.** (See XII. DRUG INTERACTIONS.)

- **Daptomycin:** Reports of myopathy and/or rhabdomyolysis have been observed with HMG-CoA reductase inhibitors coadministered with daptomycin. Caution

should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either agent can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to suspending VYTORIN temporarily in patients taking daptomycin (see XII. DRUG INTERACTIONS).

- **Ticagrelor:** The concomitant intake of VYTORIN doses of more than 10/40 mg daily with ticagrelor is not recommended (see XII. DRUG INTERACTIONS).

- **Anticoagulants:** If VYTORIN is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored (see XII. DRUG INTERACTIONS).

Myasthenia Gravis/Ocular Myasthenia
In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see XIII. SIDE EFFECTS). VYTORIN should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Liver Enzymes
In controlled coadministration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (≥ 3 X ULN) have been observed (see XIII. SIDE EFFECTS.)

In IMPROVE-IT, 18,144 patients with CHD were randomized to receive VYTORIN 10/40 mg daily(n=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of consecutive elevations of transaminases (≥ 3 X ULN) was 2.5% for VYTORIN and 2.3% for simvastatin. (See XIII. SIDE EFFECTS.)

It is recommended that LFTs be performed before treatment with VYTORIN begins and thereafter when clinically indicated. Patients titrated to the 10/80-mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 X ULN and are persistent, the drug should be discontinued. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis)*

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with VYTORIN, promptly interrupt therapy. If an alternate etiology is not found do not restart VYTORIN.

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.

Hepatic Insufficiency
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, VYTORIN is not recommended in these patients (see *IIIb-5. Characteristics in Patients [Special Populations]*).

IX. PREGNANCY

Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolemia.

VYTORIN
VYTORIN is contraindicated during pregnancy.

Simvastatin
The safety of simvastatin in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. For this reason, VYTORIN should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with VYTORIN should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see VII. CONTRAINDICATIONS).

Ezetimibe
No clinical data on exposed pregnancies are available for ezetimibe.

When ezetimibe was given with simvastatin, no teratogenic effects were observed in embryo-fetal development studies in pregnant rats. In pregnant rabbits, a low incidence of skeletal malformations was observed.

X. NURSING MOTHERS

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether the active components of VYTORIN are excreted into human breast milk; therefore, women who arenursing should not take VYTORIN.

XI. USE IN THE ELDERLY

Because advanced age (≥ 65 years) is a predisposing factor for myopathy, VYTORIN should be prescribed with caution in the elderly. In a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥ 65 years of age had an increased risk of myopathy compared to patients <65 years of age.

XII. DRUG INTERACTIONS

VYTORIN
No clinically significant pharmacokinetic interaction was seen when ezetimibe was

coadministered with simvastatin.

VYTORIN is bioequivalent to coadministered ezetimibe and simvastatin.

Multiple mechanisms may contribute to potential interactions with HMG Co-A reductase inhibitors. Drugs or herbal products that inhibit certain enzymes (e.g. CYP3A4) and/or transporter (e.g. OATP1B) pathways may increase simvastatin and simvastatin acid plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis.

Consult the prescribing information of all concomitantly used drugs to obtain further information about their potential interactions with simvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

Contraindicated drugs
Concomitant use of the following drugs is contraindicated:

Potent Inhibitors of CYP3A4
In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolizing enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolized by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase. Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations ofother drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 increase the risk of myopathy by reducing the elimination of the simvastatin component of VYTORIN: Concomitant use of drugs labeled as having a potent inhibitory effect on CYP3A4 (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, drugs containing cobicistat) is contraindicated. (See VII CONTRAINDICATIONS, VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis,* and IIIb CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Gemfibrozil, Cyclosporine, or Danazol (see VII. CONTRAINDICATIONS and VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis).*

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. This increase is not considered clinically significant. No clinical data are available. (See VII. CONTRAINDICATIONS and VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis.*)

Cyclosporine: In a study of eight post-renal transplant patients with creatinine clearance of >50 mL/min on a stable dose of cyclosporine, a single 10-mg dose of ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of cyclosporine alone (see VII. CONTRAINDICATIONS and VIII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Other drug interactions

Other Fibrates: The safety and effectiveness of VYTORIN administered with fibrates have

not been studied.

Simvastatin - Fibrates can cause myopathy when given alone. Severe myositis with myoglobinuria has been reported with concomitant use of statins and fibrates. Therefore, the concomitant use of VYTORIN and fibrates, should be avoided. Concomitant use of gemfibrozil is contraindicated (see VII. CONTRAINDICATIONS)
Ezetimibe – Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. Coadministration of ezetimibe with other fibrates has not been studied. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, coadministration of VYTORIN with fibrates, is not recommended until use in patients is studied.

Fusidic Acid: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of fusidic acid (see VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Amiodarone: The risk of myopathy/rhabdomyolysis is increased by concomitant administration ofamiodarone with VYTORIN (see V. DOSAGE AND ADMINISTRATION and VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

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

Calcium Channel Blockers: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine (see V. DOSAGE AND ADMINISTRATION and VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Lomitapide: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide (see V. DOSAGE AND ADMINISTRATION and VIII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Moderate Inhibitors of CYP3A4: Patients taking other medicines labeled as having a moderate inhibitory effect on CYP3A4 concomitantly with VYTORIN, particularly higher VYTORIN doses may have an increased risk of myopathy (see VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Inhibitors of the Transport Protein OATP1B1: Simvastatin acid is a substrate of the transport protein OATP1B1. Concomitant administration of medicinal products that are inhibitors of the transport protein OATP1B1 may lead to increased plasma concentrations of simvastatin acid and an increased risk of myopathy. (see VII. CONTRAINDICATIONS; VIII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Inhibitors of Breast Cancer Resistant Protein (BCRP): Simvastatin is a substrate of the efflux transporter BCRP. Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy. When coadministering simvastatin with an inhibitor of BCRP, a dose adjustment of VYTORIN may be necessary (see V. DOSAGE AND ADMINISTRATION, VIII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Niacin: In a study of 15 healthy adults, concomitant VYTORIN (10/20 mg daily for 7 days) caused a small increase in the mean AUCs of niacin (22%) and nicotinuric acid (19%) administered as NIASPAN extended-release tablets (1000 mg for 2 days and 2000 mg for 5

days following a low-fat breakfast). In the same study, concomitant NIASPAN slightly increased the mean AUCs of ezetimibe (9%), total ezetimibe (26%), simvastatin (20%) and simvastatin acid (35%).
Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥ 1 g/day) of niacin (see VIII. PRECAUTIONS, Myopathy/Rhabdomyolysis).

Colchicine: There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and VYTORIN in patients with renal insufficiency. Close clinical monitoring of such patients taking this combination is advised.

Daptomycin: The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors and daptomycin (see VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Ticagrelor: Co-administration of ticagrelor with simvastatin increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2- to 3-fold. Co-administration of ticagrelor with doses of simvastatin exceeding 40 mg daily could cause adverse reactions of simvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. The concomitant use of ticagrelor with doses of simvastatin greater than 40 mg is not recommended.

Other Interactions
Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of drugs metabolized by CYP3A4. The effect of typical consumption (one 250-mL glass daily) is minimal (13% increase in active plasma HMG-CoA reductase inhibitory activity as measured by the area under the concentration-time curve) and of no clinical relevance. However, because larger quantities significantly increase the plasma levels of HMG-CoA reductase inhibitory activity, grapefruit juice should be avoided during VYTORIN therapy (see VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Anticoagulants
In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, 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 the volunteer and patient studies, respectively. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting VYTORIN and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of VYTORIN is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

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

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

Antacids: Concomitant antacid administration decreased the rate of absorption of ezetimibe

but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

XIII. SIDE EFFECTS

VYTORIN (or coadministration of ezetimibe and simvastatin equivalent to VYTORIN) has been evaluated for safety in approximately 12,000 patients in clinical trials. VYTORIN was generally well tolerated.

The following common (≥1/100, <1/10) or uncommon (≥1/1000, <1/100); drug-related adverse experiences were reported in patients taking VYTORIN (n=2404) and at a greater incidence than placebo (n=1340):

Investigations:
Common: ALT and/or AST increased; blood CK increased
Uncommon: blood bilirubin increased; blood uric acid increased; gamma-glutamyltransferase increased; international normalised ratio increased; protein urine present; weight decreased

Nervous system disorders:
Uncommon: dizziness; headache

Gastrointestinal disorders:
Uncommon: abdominal pain; abdominal discomfort; abdominal pain upper; dyspepsia; flatulence;nausea; vomiting

Skin and subcutaneous tissue disorders:
Uncommon: pruritus; rash

Musculoskeletal and connective tissue disorders:
Uncommon: arthralgia; muscle spasms; muscular weakness; musculoskeletal discomfort; neckpain; pain in extremity

General disorders and administration site conditions:
Uncommon: asthenia; fatigue; malaise; edema peripheral

Psychiatric disorders:
Uncommon: sleep disorders

The following common (≥ 1/100, <1/10) or uncommon (≥1/1000, <1/100); drug-related adverse experiences were reported in patients taking VYTORIN (n=9595) and at a greater incidence than statins administered alone (n=8883):

Investigations:
Common: ALT and/or AST increased
Uncommon: blood bilirubin increased; blood CK increased; gamma-glutamyltransferase increased

Nervous system disorders:
Uncommon: headache; paresthesia

Gastrointestinal disorders:
Uncommon: abdominal distension; diarrhea; dry mouth; dyspepsia; flatulence;

gastroesophagealreflux disease; vomiting

Skin and subcutaneous tissue disorders:
Uncommon: pruritus; rash; urticaria

Musculoskeletal and connective tissue disorders:
Common: myalgia
Uncommon: arthralgia; back pain; muscle spasms; muscular weakness; musculoskeletal pain;pain in extremity

General disorders and administration site conditions:
Uncommon: asthenia; chest pain; fatigue; edema peripheral

Psychiatric disorders:
Uncommon: insomnia

Patients with Coronary Heart Disease
In the IMPROVE-IT study (see *VI. Clinical Studies*), involving 18,144 patients treated with either VYTORIN 10/40 mg (n=9067; of whom 6% were uptitrated to VYTORIN 10/80 mg) or simvastatin40 mg (n=9077; of whom 27% were uptitrated to simvastatin 80 mg), the safety profiles were similar during a median follow-up period of 6.0 years. Discontinuation rates due to adverse experiences were 10.6% for patients treated with VYTORIN and 10.1% for patients treated with simvastatin. The incidence of myopathy was 0.2% for VYTORIN and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 timesULN or two consecutive observations of CK ≥ 5 and <10 times ULN. The incidence of rhabdomyolysis was 0.1% for VYTORIN and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN with evidence of renal injury, ≥ 5 X ULN and <10 X ULN on two consecutive occasions with evidence of renal injury or CK ≥ 10,000 IU/L without evidence of renal injury. The incidence of consecutive elevations of transaminases (≥ 3 X ULN) was 2.5% for VYTORIN and 2.3% for simvastatin. (See VIII. PRECAUTIONS.) Gallbladder-related adverse effects were reported in 3.1% vs 3.5% of patients allocated to VYTORIN and simvastatin, respectively. The incidence of cholecystectomy hospitalizations was 1.5% in both treatment groups. Cancer (defined as any new malignancy) was diagnosed during the trial in 9.4% vs 9.5%, respectively.

Post-marketing Experience
The following additional adverse reactions have been reported in post-marketing use with VYTORIN or during clinical studies or post-marketing use with one of the individual components. The adverse reactions reported for VYTORIN are consistent with those previously reported with ezetimibe and/or simvastatin.

Investigations: liver function test abnormal

Blood and lymphatic system disorders: thrombocytopenia; anemia

Nervous system disorders: peripheral neuropathy;
Frequency 'not known': myasthenia gravis (see VIII. PRECAUTIONS*, Myasthenia Gravis/Ocular Myasthenia*).

Eye disorders:
Frequency 'not known': ocular myasthenia *(*see VIII. PRECAUTIONS*, Myasthenia Gravis/Ocular Myasthenia*).

Respiratory, thoracic and mediastinal disorders: cough; interstitial lung disease

Gastrointestinal disorders: constipation; pancreatitis; gastritis

Skin and subcutaneous tissue disorders: alopecia; hypersensitivity reactions, including rash, lichenoid drug eruptions, urticaria, anaphylaxis, angio-edema; severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilic and systemic symptoms (DRESS) and erythema multiforme

Musculoskeletal and connective tissue disorders: muscle cramps; myopathy/rhabdomyolysis (see VIII. PRECAUTIONS, *Myopathy/Rhabdomyolysis*)

There have been very rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is clinically characterized by: persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents (see VIII PRECAUTIONS, *Myopathy/Rhabdomyolysis)*.

Metabolism and nutrition disorders: decreased appetite

Vascular disorders: hot flush; hypertension

General disorders and administration site conditions: pain

Hepato-biliary disorders: hepatitis/jaundice; fatal and non-fatal hepatic failure; cholelithiasis;cholecystitis; drug-induced liver injury

Reproductive system and breast disorders: erectile dysfunction

Psychiatric disorders: depression

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnea and malaise.

There have been rare post marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Laboratory Values
In controlled clinical coadministration trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was 1.7% for patients treated with VYTORIN. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see VIII. PRECAUTIONS).

Clinically important elevations of CK (≥ 10 X ULN) were seen in 0.2% of the patients treated with VYTORIN.

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including simvastatin. The risk of hyperglycemia, however, is outweighed by the reduction in

vascular risk with statins.

XIV. OVERDOSAGE

VYTORIN
No specific treatment of overdosage with VYTORIN can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed. Coadministration of ezetimibe (1000 mg/kg) and simvastatin (1000 mg/kg) was well-tolerated in acute, oral toxicity studies in mice and rats. No clinical signs of toxicity were observed in these animals. The estimated oral LD_{50} for both species was ezetimibe ≥ 1000 mg/kg/simvastatin ≥ 1000 mg/kg.

Ezetimibe
In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, and 40 mg/day to 27 patients with homozygous sitosterolemia for 26 weeks, was generally welltolerated.

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

Simvastatin
A few cases of overdosage have been reported; the maximum dose taken was 3.6 g. All patientsrecovered without sequelae.

XV. STORAGE

Do not store above 30°C, usual climatic temperature excursions permitted.

XVI. AVAILABILITY

VYTORIN 10/10mg Tablet: Available in aluminium cold formable foil blister packs of 10's and 30's per pack.

VYTORIN 10/20 and 10/40 Tablet: Available in white opaque PVC/Aclar blister packs of 10's and 30's per pack.

XVII. PHYSICAL APPEARANCE

VYTORIN 10/10mg Tablet: White to off-white, capsule shaped, biconvex compressed tablet with marking 311.

VYTORIN 10/20mg Tablet: White to off-white, capsule shaped, biconvex compressed tablet with marking 312.

VYTORIN 10/40mg Tablet: White to off-white, capsule shaped, biconvex compressed tablet with marking 313.

XVIII. SHELF LIFE

Please refer to the expiry date on the outer carton.

XIX. MANUFACTURER

Organon Pharma (UK) Limited
Shotton Lane, Cramlington
NE23 3JU
United Kingdom.

XX. PRODUCT REGISTRATION HOLDER

ORGANON MALAYSIA SDN. BHD.
3A-08-02, Level 8, Corporate Tower 3A,
Pavilion Damansara Heights,
No. 3, Jalan Damanlela
50490 Kuala Lumpur, Malaysia.

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