



Zocor[®] (simvastatin)
Vytorin[®] (ezetimibe/simvastatin)

June 8, 2011

Subject: Restricted dosing of simvastatin 80-mg dose and updated drug interaction information due to dose-related risk of myopathy/rhabdomyolysis

Dear Health Care Professional:

The Prescribing Information for the above medicines has changed. The changes are based on an increased risk of myopathy, including rhabdomyolysis, with simvastatin 80 mg compared with other statin therapies with similar or greater LDL-C-lowering efficacy and compared with lower doses of simvastatin. This increased risk is highest during the first year of treatment and notably decreases thereafter. Simvastatin 80 mg should not be started in new patients.

What are the label updates?

- Use of the 80-mg dose of simvastatin should be restricted to patients who have been taking that dose chronically (eg, for 12 months or more) without evidence of muscle toxicity.
- Due to the potential for drug interactions, concomitant use of the following medications with any available dose of simvastatin is now contraindicated:

<i>Interacting drug</i>	<i>Previous label</i>	<i>Updated label</i>
Strong CYP3A4 inhibitors (eg, itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, and nefazodone)	Avoid	Contraindicated; posaconazole added to list of examples
Gemfibrozil, cyclosporine, danazol	Do not exceed 10-mg simvastatin daily	Contraindicated

- Other medications should not be administered with certain doses of simvastatin due to potential drug interactions. These medications and corresponding dosing instructions (referred to as dose caps) are:

<i>Interacting drug</i>	<i>Previous label</i>	<i>Updated label</i>
Amiodarone Verapamil	Do not exceed 20-mg simvastatin daily	Do not exceed 10-mg simvastatin daily
Diltiazem	Do not exceed 40-mg simvastatin daily	Do not exceed 10-mg simvastatin daily
Amlodipine Ranolazine	No dose cap	Do not exceed 20-mg simvastatin daily

- Patients continuing on simvastatin 80 mg who need to be initiated on one or more medications that are subject to a contraindication or dose cap should be switched to an alternative statin with less potential for the drug interaction. Patients taking *Vytorin*[®] (ezetimibe/simvastatin) 10/80 mg who need to add one or more of these medications should be switched to an alternative statin or statin-based regimen with less potential for the drug interaction.
- Patients unable to achieve their LDL-C goal utilizing simvastatin 40 mg or *Vytorin* 10/40 mg should not be titrated to simvastatin 80 mg or *Vytorin* 10/80 mg, respectively, but should be placed on alternative LDL-C–lowering treatment(s) that provides greater LDL-C lowering.
- The recommended starting dose for simvastatin is 10 mg or 20 mg once daily in the evening and for *Vytorin* is 10/10 mg or 10/20 mg once daily in the evening. Patients taking simvastatin who are at high risk of a coronary heart disease (CHD) event and patients taking *Vytorin* who require a larger reduction in LDL-C (greater than 55%) may be started at simvastatin 40 mg once daily or *Vytorin* 10/40 mg once daily, respectively.

Enclosed with this letter are copies of the full Prescribing Information for *Zocor*[®] (simvastatin) and the full Prescribing Information and Patient Information for *Vytorin*. Specific areas where changes have occurred in the Prescribing Information for *Zocor* and *Vytorin* are noted.

How do these changes affect management of patients who already take simvastatin or *Vytorin*?

Assess whether patients who are currently taking simvastatin or *Vytorin* need their regimens adjusted; many patients will not be affected.

<i>If patient takes...</i>	<i>With...</i>	<i>Adjust as follows...</i>
Simvastatin 80 mg <i>Or</i> <i>Vytorin</i> 10/80 mg	<u>No</u> interacting drugs	No adjustment if patient has been taking simvastatin 80 mg or <i>Vytorin</i> 10/80 mg chronically (eg, for 12 months or more) without evidence of muscle toxicity.
	An interacting drug	If the interacting drug is needed, switch patient to an alternative statin with less potential for the drug-drug interaction, in the case of simvastatin, or to an alternative statin or statin-based regimen with less potential for the drug-drug interaction, in the case of <i>Vytorin</i> .
Simvastatin 5 mg to 40 mg <i>Or</i> <i>Vytorin</i> 10/10 mg to 10/40 mg	<u>No</u> interacting drugs	No adjustment.
	An interacting drug	Adjust regimen in accordance with Prescribing Information to reduce the potential for the drug-drug interaction.
Simvastatin 40 mg or <i>Vytorin</i> 10/40 mg and is unable to achieve LDL-C goal		Do not titrate patient to simvastatin 80 mg or <i>Vytorin</i> 10/80 mg, respectively. Place patient on alternative LDL-C–lowering treatment(s) that provides greater LDL-C lowering.

Continue to monitor all patients for potential side effects according to Prescribing Information. Tell patients to report promptly any unexplained muscle pain, tenderness, or weakness.

What new clinical data are included in the labels regarding myopathy/rhabdomyolysis?

In a clinical trial called SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] >10 times upper limit of normal [ULN]) in patients on simvastatin 80 mg/day was approximately 0.9% compared with 0.02% for patients on 20 mg/day. The incidence of rhabdomyolysis (defined as myopathy with a CK >40 times ULN) in patients on 80 mg/day was approximately 0.4% compared with 0% for patients on 20 mg/day. The incidence of myopathy, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent years of treatment. The changes to the Prescribing Information for *Zocor*[®] (simvastatin) and *Vytorin*[®] (ezetimibe/simvastatin) follow a review by the US FDA of data from SEARCH and other sources, including information about other statins.

Additional Information

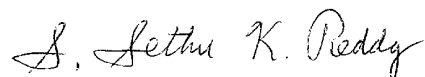
Merck has created the attached patient resource and a special Web site, www.simvastatininfocenter.com, with information for patients about these updates. The patient resource is also available at that Web site.

Nothing is more important to Merck than the safety of our medicines and vaccines. Merck encourages health care providers and consumers to report any adverse experience associated with any Merck medication or vaccine. Adverse events can be reported to the Merck National Service Center (1-800-672-6372), FDA MedWatch (online at www.fda.gov/medwatch or by phone at 1-800-FDA-1088), or your Merck representative.

If you have additional questions, please contact Merck at 1-800-235-1434 or your Merck representative.

Before prescribing *Zocor* or *Vytorin*, please read the accompanying Prescribing Information.

Sincerely,



S. Sethu K. Reddy, MD, MBA, FRCPC, FACP, MACE
Vice President, Head - US Medical Affairs
Merck

Enclosures:

- Prescribing Information for *Zocor*
- Prescribing Information and Patient Information for *Vytorin*
- Patient resource

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CARD-1002092-0001 06/11

Information for Patients About Recent Changes to the Prescribing Recommendations for Simvastatin and *Vytorin*[®] (ezetimibe/simvastatin)

Simvastatin is available in generic form and under the brand name *Zocor*[®].
Simvastatin is also contained in the combination medicine *Vytorin*.

Who is affected by the changes to the prescribing recommendations for simvastatin and *Vytorin*?

Some people taking these medicines will be affected and others will not. Changes to the prescribing recommendations affect:

- People who take the highest dose of simvastatin (80 mg) or the highest dose of *Vytorin* (10/80 mg). These doses should only be used by people who have been taking them chronically (such as 12 months or more) without having muscle damage. There is an increased risk of muscle damage with the highest dose, especially during the first year of use.
- People who take simvastatin or *Vytorin* at any dose who also take certain other medicines that can increase the risk of muscle problems. See “*What medicines cannot be taken with any dose of simvastatin or Vytorin?*” and “*What other medicines or substances might affect my prescription for simvastatin or Vytorin?*”

Other people are not affected by these changes to the prescribing recommendations.

For more information about the risk of muscle problems, please read “*What are the muscle problems associated with simvastatin?*”.

I currently take simvastatin or *Vytorin* and think the changes to the prescribing recommendations might affect me. What should I do?

If you think you may be affected by these changes, talk to your doctor. Your doctor will determine whether you are affected by these changes or not. You should talk to your doctor before you stop taking any medicines.

Tell your doctor about all the medicines you take, including any prescription and nonprescription medicines, vitamins, and herbal supplements. This will help your doctor decide if changes should be made to any of the medicines you may be taking.

If your doctor decides that your current dose of simvastatin or *Vytorin* is still right for you, continue to take your medicine as prescribed.

What medicines cannot be taken with any dose of simvastatin or *Vytorin*?

Do not take simvastatin or *Vytorin* if you also take:

- Certain antifungal medicines, including itraconazole, ketoconazole, or posaconazole
- HIV protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir, tipranavir, or atazanavir)
- Certain antibiotics, including erythromycin, clarithromycin, or telithromycin
- Nefazodone
- Gemfibrozil, a fibric acid medicine for lowering cholesterol
- Cyclosporine
- Danazol

Taking simvastatin or *Vytorin* with these medicines can increase the risk of muscle problems. If you are not sure whether a medicine you take should not be taken with simvastatin or *Vytorin*, ask your doctor.

What other medicines or substances might affect my prescription for simvastatin or *Vytorin*?

Because of an increased risk of muscle problems, it is important to tell your doctor if you take:

- Fibric acid derivatives (such as fenofibrate)
- Amiodarone (a drug used to treat an irregular heartbeat)
- Verapamil, diltiazem, amlodipine, or ranolazine (drugs used to treat high blood pressure, chest pain associated with heart disease or other heart conditions)
- Large quantities of grapefruit juice (more than 1 quart daily)
- Colchicine (a medicine used to treat gout)
- Voriconazole (an antifungal medicine)
- Large doses of niacin or nicotinic acid

Tell your doctor if you are taking niacin or a niacin-containing product as this may increase your risk of muscle problems, especially if you are Chinese.

It is also important to tell your doctor if you are taking coumarin anticoagulants (drugs that prevent blood clots, such as warfarin).

Why are the prescribing recommendations being changed?

Earlier prescribing recommendations have explained that the risk of muscle problems with simvastatin, including in rare cases muscle breakdown, is greater at higher doses. The prescribing recommendations have been updated over time to reflect new safety information.

The most recent update follows an FDA review of the risk of muscle problems with high-dose simvastatin. That review was based on information that Merck reported to the FDA from a clinical study of the highest dose of simvastatin (80 mg), as well as on information from other sources.

What are the muscle problems associated with simvastatin?

Simvastatin sometimes causes muscle problems, such as muscle pain, tenderness, or weakness. Muscle problems, including muscle breakdown, can be serious in some people and rarely cause kidney damage that can lead to death.

The risk of muscle breakdown with simvastatin is greater when taking higher doses, particularly the 80-mg dose of simvastatin or the 10/80-mg dose of *Vytorin*[®] (ezetimibe/simvastatin). The risk with the highest dose is greatest during the first year of use. At any dose, the risk of muscle breakdown is also greater in people 65 years of age or older, females, people with kidney or thyroid problems, and with the use of certain medicines. **Tell your doctor right away if you experience unexplained muscle pain, tenderness, or weakness.**

What other important risk information should I know about simvastatin and *Vytorin*?

Simvastatin and *Vytorin* should not be taken by women who are nursing or pregnant or who may become pregnant, by anyone with liver problems, or by people who are allergic to any ingredients of these medicines.

Your doctor may do simple blood tests before and during treatment to check for liver problems.

In clinical trials of *Zocor*[®] (simvastatin), side effects included upper respiratory infections, headache, abdominal pain, constipation, and nausea.

In clinical trials of *Vytorin*, side effects included headache, muscle pain, and diarrhea.

This is not a complete list of all risks associated with simvastatin or *Vytorin*.

What is simvastatin?

Simvastatin is a prescription medicine that is used along with diet to improve cholesterol levels in people with high cholesterol when diet alone is not enough. In patients with heart disease or diabetes, simvastatin, along with a healthy diet, is also used to reduce the risk of heart attack and stroke.

Simvastatin is widely available in generic form and is also available under the brand name *Zocor*. The FDA is changing the prescribing recommendations for *Zocor* as well as for generic simvastatin.

What is *Vytorin*?

Vytorin is a prescription medicine that contains two cholesterol medicines, ezetimibe and simvastatin, in a single tablet. *Vytorin* is used along with diet to improve cholesterol levels in people with high cholesterol when diet alone is not enough. *Vytorin* has not been shown to reduce heart attacks or strokes more than simvastatin alone.

Because *Vytorin* contains simvastatin, recent changes to prescribing recommendations for simvastatin regarding the risk of muscle problems also apply to *Vytorin*.

If I have more questions about simvastatin or *Vytorin*, where should I go for information?

Talk with your doctor. If you have high cholesterol, it is important to stay on a healthy diet and to follow your doctor's instructions on how to manage your high cholesterol.

Please read the accompanying Product Information for *Zocor* and *Vytorin*, including Patient Information for *Vytorin*, and discuss it with your doctor.

This information is also available at www.simvastatininfocenter.com.



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CARD-1002092-0002 06/11

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOCOR safely and effectively. See full prescribing information for ZOCOR.

ZOCOR (simvastatin) Tablets

Initial U.S. Approval: 1991

RECENT MAJOR CHANGES

Dosage and Administration	
Recommended Dosing (2.1)	06/2011
Restricted Dosing for 80 mg (2.2)	06/2011
Coadministration with Other Drugs (2.3)	06/2011
Patients with Homozygous Familial Hypercholesterolemia (2.4)	
Chinese Patients Taking Lipid-Modifying Doses (≥1 g/day Niacin) of Niacin-Containing Products (2.7)	06/2011
Contraindications (4)	06/2011
Warnings and Precautions	
Myopathy/Rhabdomyolysis (5.1)	06/2011
Liver Dysfunction (5.2)	06/2011

INDICATIONS AND USAGE

ZOCOR[®] is an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to:

- Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events. (1.1)
- Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia. (1.2)
- Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbeta-lipoproteinemia. (1.2)
- Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia. (1.2)
- Reduce elevated total-C, LDL-C, and Apo B in boys and postmenarchal girls, 10 to 17 years of age with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy. (1.2, 1.3)

Limitations of Use

ZOCOR has not been studied in Fredrickson Types I and V dyslipidemias. (1.4)

DOSAGE AND ADMINISTRATION

- Dose range is 5 to 40 mg/day. (2.1)
- Recommended usual starting dose is 10 or 20 mg once a day in the evening. (2.1)
- Recommended starting dose for patients at high risk of CHD is 40 mg/day. (2.1)
- Due to the increased risk of myopathy, including rhabdomyolysis, use of the 80-mg dose of ZOCOR should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. (2.2)
- Patients who are currently tolerating the 80-mg dose of ZOCOR who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin with less potential for the drug-drug interaction. (2.2)
- Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 80-mg dose of ZOCOR, patients unable to achieve their LDL-C goal utilizing the 40-mg dose of ZOCOR should not be titrated to the 80-mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering. (2.2)
- Adolescents (10-17 years of age) with HeFH: starting dose is 10 mg/day; maximum recommended dose is 40 mg/day. (2.5)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg; 10 mg; 20 mg; 40 mg; 80 mg (3)

CONTRAINDICATIONS

- Concomitant administration of strong CYP3A4 inhibitors. (4, 5.1)
- Concomitant administration of gemfibrozil, cyclosporine, or danazol. (4, 5.1)
- Hypersensitivity to any component of this medication. (4, 6.2)
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels. (4, 5.2)
- Women who are pregnant or may become pregnant. (4, 8.1)
- Nursing mothers. (4, 8.3)

WARNINGS AND PRECAUTIONS

- **Patients should be advised of the increased risk of myopathy including rhabdomyolysis with the 80-mg dose. (5.1)**
- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain medicines. Predisposing factors include advanced age (≥65), female gender, uncontrolled hypothyroidism, and renal impairment. (4, 5.1, 8.5, 8.6)
- Patients should be advised to report promptly any symptoms of myopathy. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. See Drug Interaction table. (5.1)
- Liver enzyme abnormalities and monitoring: Persistent elevations in hepatic transaminase can occur. Monitor liver enzymes before and during treatment. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5.0%) are: upper respiratory infection, headache, abdominal pain, constipation, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.3, 4, 5.1, 7.1, 7.2, 7.3, 12.3)

Interacting Agents	Prescribing Recommendations
Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol	Contraindicated with simvastatin
Amiodarone, verapamil, diltiazem	Do not exceed 10 mg simvastatin daily
Amlodipine, ranolazine	Do not exceed 20 mg simvastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

- Coumarin anticoagulants: Concomitant use with ZOCOR prolongs INR. Achieve stable INR prior to starting ZOCOR. Monitor INR frequently until stable upon initiation or alteration of ZOCOR therapy. (7.6)

USE IN SPECIFIC POPULATIONS

- Severe renal impairment: patients should be started at 5 mg/day and be closely monitored. (2.6, 8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2011

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FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE**

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with coronary heart disease (CHD) or at high risk of CHD, ZOCOR¹ can be started simultaneously with diet.

1.1 Reductions in Risk of CHD Mortality and Cardiovascular Events

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, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures.

1.2 Hyperlipidemia

ZOCOR is indicated to:

- Reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hyperlipidemia (Fredrickson type IIa, heterozygous familial and nonfamilial) or mixed dyslipidemia (Fredrickson type IIb).
- Reduce elevated TG in patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia).
- Reduce elevated TG and VLDL-C in patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

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1.3 Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH)

ZOCOR is indicated as an adjunct to diet to reduce total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with HeFH, if after an adequate trial of diet therapy the following findings are present:

1. LDL cholesterol remains ≥ 190 mg/dL; or
2. LDL cholesterol remains ≥ 160 mg/dL and
 - There is a positive family history of premature cardiovascular disease (CVD) or
 - Two or more other CVD risk factors are present in the adolescent patient.

The minimum goal of treatment in pediatric and adolescent patients is to achieve a mean LDL-C < 130 mg/dL. The optimal age at which to initiate lipid-lowering therapy to decrease the risk of symptomatic adulthood CAD has not been determined.

1.4 Limitations of Use

ZOCOR has not been studied in conditions where the major abnormality is elevation of chylomicrons (i.e., hyperlipidemia Fredrickson types I and V).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The usual dosage range is 5 to 40 mg/day. In patients with CHD or at high risk of CHD, ZOCOR can be started simultaneously with diet. The recommended usual starting dose is 10 or 20 mg once a day in the evening. For patients at high risk for a CHD event due to existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter.

2.2 Restricted Dosing for 80 mg

Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80-mg dose of ZOCOR should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity [see *Warnings and Precautions (5.1)*].

Patients who are currently tolerating the 80-mg dose of ZOCOR who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin with less potential for the drug-drug interaction.

Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 80-mg dose of ZOCOR, patients unable to achieve their LDL-C goal utilizing the 40-mg dose of ZOCOR should not be titrated to the 80-mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering.

2.3 Coadministration with Other Drugs

Patients taking Amiodarone, Verapamil, or Diltiazem

- The dose of ZOCOR should not exceed 10 mg/day [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.3)*, and *Clinical Pharmacology (12.3)*].

Patients taking Amlodipine or Ranolazine

- The dose of ZOCOR should not exceed 20 mg/day [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.3)*, and *Clinical Pharmacology (12.3)*].

2.4 Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage is 40 mg/day in the evening [see *Dosage and Administration, Restricted Dosing for 80 mg (2.2)*]. ZOCOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

2.5 Adolescents (10-17 years of age) with Heterozygous Familial Hypercholesterolemia

The recommended usual starting dose is 10 mg once a day in the evening. The recommended dosing range is 10 to 40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be

individualized according to the recommended goal of therapy [see NCEP Pediatric Panel Guidelines² and *Clinical Studies (14.2)*]. Adjustments should be made at intervals of 4 weeks or more.

2.6 Patients with Renal Impairment

Because ZOCOR does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal impairment. However, caution should be exercised when ZOCOR is administered to patients with severe renal impairment; such patients should be started at 5 mg/day and be closely monitored [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

2.7 Chinese Patients Taking Lipid-Modifying Doses (≥ 1 g/day Niacin) of Niacin-Containing Products

Because of an increased risk for myopathy in Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products, caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products. The cause of the increased risk of myopathy is not known. It is also unknown if the risk for myopathy with coadministration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients. [See *Warnings and Precautions (5.1)*.]

3 DOSAGE FORMS AND STRENGTHS

- Tablets ZOCOR 5 mg are buff, oval, film-coated tablets, coded MSD 726 on one side and ZOCOR 5 on the other.
- Tablets ZOCOR 10 mg are peach, oval, film-coated tablets, coded MSD 735 on one side and plain on the other.
- Tablets ZOCOR 20 mg are tan, oval, film-coated tablets, coded MSD 740 on one side and plain on the other.
- Tablets ZOCOR 40 mg are brick red, oval, film-coated tablets, coded MSD 749 on one side and plain on the other.
- Tablets ZOCOR 80 mg are brick red, capsule-shaped, film-coated tablets, coded 543 on one side and 80 on the other.

4 CONTRAINDICATIONS

ZOCOR is contraindicated in the following conditions:

- Concomitant administration of strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) [see *Warnings and Precautions (5.1)*].
- Concomitant administration of gemfibrozil, cyclosporine, or danazol [see *Warnings and Precautions (5.1)*].
- Hypersensitivity to any component of this medication [see *Adverse Reactions (6.2)*].
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels [see *Warnings and Precautions (5.2)*].
- Women who are pregnant or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because HMG-CoA reductase inhibitors (statins) decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, ZOCOR may cause fetal harm when administered to a pregnant woman. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome

² National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 89(3):495-501. 1992.

of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of use with ZOCOR during pregnancy; however, in rare reports congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, simvastatin revealed no evidence of teratogenicity. **ZOCOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, ZOCOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

- Nursing mothers. It is not known whether simvastatin is excreted into human milk; however, a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require treatment with ZOCOR should not breastfeed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy/Rhabdomyolysis

Simvastatin occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times 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 risk of myopathy is increased by high levels of statin activity in plasma. Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

The risk of myopathy, including rhabdomyolysis, is dose related. In a clinical trial database in which 41,413 patients were treated with ZOCOR, 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% and 0.08% at 20 and 40 mg/day, respectively. The incidence of myopathy with 80 mg (0.61%) was disproportionately higher than that observed at the lower doses. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which 12,064 patients with a history of myocardial infarction were treated with ZOCOR (mean follow-up 6.7 years), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] >10 times upper limit of normal [ULN]) in patients on 80 mg/day was approximately 0.9% compared with 0.02% for patients on 20 mg/day. The incidence of rhabdomyolysis (defined as myopathy with a CK >40 times ULN) in patients on 80 mg/day was approximately 0.4% compared with 0% for patients on 20 mg/day. The incidence of myopathy, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent years of treatment. In this trial, patients were carefully monitored and some interacting medicinal products were excluded.

The risk of myopathy, including rhabdomyolysis, is greater in patients on simvastatin 80 mg compared with other statin therapies with similar or greater LDL-C-lowering efficacy and compared with lower doses of simvastatin. Therefore, the 80-mg dose of ZOCOR should be used only in patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity [see *Dosage and Administration, Restricted Dosing for 80 mg (2.2)*]. If, however, a patient who is currently tolerating the 80-mg dose of ZOCOR needs to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin, that patient should be switched to an alternative statin with less potential for the drug-drug interaction. Patients should be advised of the increased risk of myopathy, including rhabdomyolysis, and to report promptly any unexplained muscle pain, tenderness or weakness. **If symptoms occur, treatment should be discontinued immediately.** [See *Warnings and Precautions (5.2)*.]

All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when treatment was promptly discontinued. Periodic CK determinations may

be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Drug Interactions

The risk of myopathy and rhabdomyolysis is increased by high levels of statin activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily). Combination of these drugs with simvastatin is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. [See *Contraindications (4) and Drug Interactions (7.1).*] *In vitro* studies have demonstrated a potential for voriconazole to inhibit the metabolism of simvastatin. Adjustment of the simvastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with simvastatin. [See *Drug Interactions (7.1).*]

The combined use of simvastatin with gemfibrozil, cyclosporine, or danazol is contraindicated [see *Contraindications (4) and Drug Interactions (7.1 and 7.2)*].

Caution should be used when prescribing other fibrates with simvastatin, as these agents can cause myopathy when given alone and the risk is increased when they are co-administered [see *Drug Interactions (7.2)*].

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine [see *Drug Interactions (7.7)*].

The benefits of the combined use of simvastatin with the following drugs should be carefully weighed against the potential risks of combinations: other lipid-lowering drugs (other fibrates or ≥ 1 g/day of niacin), amiodarone, verapamil, diltiazem, amlodipine, or ranolazine [see *Drug Interactions (7.3) and Table 3 in Clinical Pharmacology (12.3)*].

Cases of myopathy, including rhabdomyolysis, have been observed with simvastatin coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products. In an ongoing, double-blind, randomized cardiovascular outcomes trial, an independent safety monitoring committee identified that the incidence of myopathy is higher in Chinese compared with non-Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses of a niacin-containing product. Caution should be used when treating Chinese patients with simvastatin in doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products. It is unknown if the risk for myopathy with coadministration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients [see *Drug Interactions (7.4)*].

Prescribing recommendations for interacting agents are summarized in Table 1 [see also *Dosage and Administration (2.3), Drug Interactions (7), Clinical Pharmacology (12.3)*].

TABLE 1
Drug Interactions Associated with Increased
Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone Gemfibrozil Cyclosporine Danazol	Contraindicated with simvastatin
Amiodarone Verapamil Diltiazem	Do not exceed 10 mg simvastatin daily
Amlodipine Ranolazine	Do not exceed 20 mg simvastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

5.2 Liver Dysfunction

Persistent increases (to more than 3X the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In the Scandinavian Simvastatin Survival Study (4S) [see *Clinical Studies (14.1)*], the number of patients with more than one transaminase elevation to >3X ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1,986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, 8 (0.4%) developed consecutive LFT elevations to >3X ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 1,105 patients, the 12-month incidence of persistent hepatic transaminase elevation without regard to drug relationship was 0.9% and 2.1% at the 40- and 80-mg dose, respectively. No patients developed persistent liver function abnormalities following the initial 6 months of treatment at a given dose.

It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3X ULN or greater persist, withdrawal of therapy with ZOCOR is recommended. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy [see *Warnings and Precautions (5.1)*].

The drug 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 transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In the pre-marketing controlled clinical studies and their open extensions (2,423 patients with median duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: gastrointestinal disorders (0.5%), myalgia (0.1%), and arthralgia (0.1%). The most commonly reported adverse reactions (incidence $\geq 5\%$) in simvastatin controlled clinical trials were: upper respiratory infections (9.0%), headache (7.4%), abdominal pain (7.3%), constipation (6.6%), and nausea (5.4%).

Scandinavian Simvastatin Survival Study

In 4S involving 4,444 (age range 35-71 years, 19% women, 100% Caucasians) treated with 20-40 mg/day of ZOCOR (n=2,221) or placebo (n=2,223) over a median of 5.4 years, adverse reactions reported in $\geq 2\%$ of patients and at a rate greater than placebo are shown in Table 2.

TABLE 2
Adverse Reactions Reported Regardless of Causality by $\geq 2\%$ of Patients Treated with ZOCOR and Greater than Placebo in 4S

	ZOCOR (N = 2,221) %	Placebo (N = 2,223) %
<i>Body as a Whole</i>		
Edema/swelling	2.7	2.3
Abdominal pain	5.9	5.8
<i>Cardiovascular System Disorders</i>		
Atrial fibrillation	5.7	5.1
<i>Digestive System Disorders</i>		
Constipation	2.2	1.6
Gastritis	4.9	3.9
<i>Endocrine Disorders</i>		
Diabetes mellitus	4.2	3.6
<i>Musculoskeletal Disorders</i>		
Myalgia	3.7	3.2
<i>Nervous System/ Psychiatric Disorders</i>		
Headache	2.5	2.1
Insomnia	4.0	3.8
Vertigo	4.5	4.2
<i>Respiratory System Disorders</i>		
Bronchitis	6.6	6.3
Sinusitis	2.3	1.8
<i>Skin / Skin Appendage Disorders</i>		
Eczema	4.5	3.0
<i>Urogenital System Disorders</i>		
Infection, urinary tract	3.2	3.1

Heart Protection Study

In the Heart Protection Study (HPS), involving 20,536 patients (age range 40-80 years, 25% women, 97% Caucasians, 3% other races) treated with ZOCOR 40 mg/day (n=10,269) or placebo (n=10,267) over a mean of 5 years, only serious adverse reactions and discontinuations due to any adverse reactions were recorded. Discontinuation rates due to adverse reactions were 4.8% in patients treated with ZOCOR compared with 5.1% in patients treated with placebo. The incidence of myopathy/rhabdomyolysis was $<0.1\%$ in patients treated with ZOCOR.

Other Clinical Studies

In a clinical trial in which 12,064 patients with a history of myocardial infarction were treated with ZOCOR (mean follow-up 6.7 years), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] >10 times upper limit of normal [ULN]) in patients on 80 mg/day was approximately 0.9% compared with 0.02% for patients on 20 mg/day. The incidence of rhabdomyolysis (defined as myopathy with a CK >40 times ULN) in patients on 80 mg/day was approximately 0.4% compared with 0% for patients on 20 mg/day. The incidence of myopathy, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent

years of treatment. In this trial, patients were carefully monitored and some interacting medicinal products were excluded.

Other adverse reactions reported in clinical trials were: diarrhea, rash, dyspepsia, flatulence, and asthenia.

Laboratory Tests

Marked persistent increases of hepatic transaminases have been noted [see *Warnings and Precautions (5.2)*]. Elevated alkaline phosphatase and γ -glutamyl transpeptidase have also been reported. About 5% of patients had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK. [See *Warnings and Precautions (5.1)*.]

Adolescent Patients (ages 10-17 years)

In a 48-week, controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age (43.4% female, 97.7% Caucasians, 1.7% Hispanics, 0.6% Multiracial) with heterozygous familial hypercholesterolemia (n=175), treated with placebo or ZOCOR (10-40 mg daily), the most common adverse reactions observed in both groups were upper respiratory infection, headache, abdominal pain, and nausea [see *Use in Specific Populations (8.4)* and *Clinical Studies (14.2)*].

6.2 Post-Marketing Experience

Because the below reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following additional adverse reactions have been identified during postapproval use of simvastatin: pruritus, alopecia, a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails), dizziness, muscle cramps, myalgia, pancreatitis, memory impairment, paresthesia, peripheral neuropathy, vomiting, anemia, erectile dysfunction, interstitial lung disease, rhabdomyolysis, hepatitis/jaundice, hepatic failure, and depression.

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

7 DRUG INTERACTIONS

7.1 Strong CYP3A4 Inhibitors, cyclosporine, or danazol

Strong CYP3A4 inhibitors: Simvastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of CYP3A4. Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4.

Elevated plasma levels of HMG-CoA reductase inhibitory activity increases the risk of myopathy and rhabdomyolysis, particularly with higher doses of simvastatin. [See *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*.] Concomitant use of drugs labeled as having a strong inhibitory effect on CYP3A4 is contraindicated [see *Contraindications (4)*]. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment.

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of simvastatin. It is recommended that dose adjustment of simvastatin be considered during concomitant use of voriconazole and simvastatin to reduce the risk of myopathy, including rhabdomyolysis. [see *Warnings and Precautions (5.1)*]

Cyclosporine or Danazol: The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol. Therefore, concomitant use of these drugs is contraindicated. [see *Contraindications (4)*, *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

7.2 Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

Gemfibrozil: Contraindicated with simvastatin [see *Contraindications (4) and Warnings and Precautions (5.1)*].

Other fibrates: Caution should be used when prescribing with simvastatin [see *Warnings and Precautions (5.1)*].

7.3 Amiodarone, Ranolazine, or Calcium Channel Blockers

The risk of myopathy, including rhabdomyolysis, is increased by concomitant administration of amiodarone, ranolazine, or calcium channel blockers such as verapamil, diltiazem, or amlodipine [see *Dosage and Administration (2.3) and Warnings and Precautions (5.1), and Table 3 in Clinical Pharmacology (12.3)*].

7.4 Niacin

Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products. In particular, caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products. [See *Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*.]

7.5 Digoxin

In one study, concomitant administration of digoxin with simvastatin resulted in a slight elevation in digoxin concentrations in plasma. Patients taking digoxin should be monitored appropriately when simvastatin is initiated [see *Clinical Pharmacology (12.3)*].

7.6 Coumarin 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. With other statins, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin 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 simvastatin 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.

7.7 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [See Contraindications (4).]

ZOCOR is contraindicated in women who are or may become pregnant. Lipid lowering drugs offer no benefit during pregnancy, because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy. There are no adequate and well-controlled studies of use with ZOCOR during pregnancy; however, there are rare reports of congenital anomalies in infants exposed to statins *in utero*. Animal reproduction studies of simvastatin in rats and rabbits showed no evidence of teratogenicity. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because statins decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, ZOCOR may cause fetal harm when

administered to a pregnant woman. If ZOCOR is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

There are rare reports of congenital anomalies following intrauterine exposure to statins. In a review³ of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related statin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed those expected in the general population. However, the study was only able to exclude a 3- to 4-fold increased risk of congenital anomalies over the background rate. In 89% of these cases, drug treatment was initiated prior to pregnancy and was discontinued during the first trimester when pregnancy was identified.

Simvastatin was not teratogenic in rats or rabbits at doses (25, 10 mg/kg/day, respectively) that resulted in 3 times the human exposure based on mg/m² surface area. However, in studies with another structurally-related statin, skeletal malformations were observed in rats and mice.

Women of childbearing potential, who require treatment with ZOCOR for a lipid disorder, should be advised to use effective contraception. For women trying to conceive, discontinuation of ZOCOR should be considered. If pregnancy occurs, ZOCOR should be immediately discontinued.

8.3 Nursing Mothers

It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants. A decision should be made whether to discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother [see *Contraindications (4)*].

8.4 Pediatric Use

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse reaction profile similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no significant effect on growth or sexual maturation in the adolescent boys or girls, or on menstrual cycle length in girls. [See *Dosage and Administration (2.5)*, *Adverse Reactions (6.1)*, *Clinical Studies (14.2)*.] Adolescent females should be counseled on appropriate contraceptive methods while on simvastatin therapy [see *Contraindications (4)* and *Use in Specific Populations (8.1)*]. Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

8.5 Geriatric Use

Of the 2,423 patients who received ZOCOR in Phase III clinical studies and the 10,269 patients in the Heart Protection Study who received ZOCOR, 363 (15%) and 5,366 (52%), respectively were ≥65 years old. In HPS, 615 (6%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, ZOCOR should be prescribed with caution in the elderly. [See *Clinical Pharmacology (12.3)*.]

A pharmacokinetic study with simvastatin showed the mean plasma level of statin activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age. In 4S, 1,021 (23%) of 4,444 patients were 65 or older. Lipid-lowering efficacy was at least as great in elderly patients compared with younger patients, and ZOCOR significantly reduced total mortality and CHD mortality in elderly patients with a history of CHD. In HPS, 52% of patients were elderly (4,891 patients 65-69 years and 5,806 patients 70 years or older). The relative risk reductions of CHD death, non-fatal MI, coronary and non-coronary revascularization procedures, and stroke were similar in older and younger patients [see *Clinical Studies (14.1)*]. In HPS, among 32,145 patients entering the active run-in period, there were 2 cases of myopathy/rhabdomyolysis; these patients were aged 67 and 73. Of the 7 cases of

³ Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy, *Reproductive Toxicology*, 10(6):439-446, 1996.

myopathy/rhabdomyolysis among 10,269 patients allocated to simvastatin, 4 were aged 65 or more (at baseline), of whom one was over 75. There were no overall differences in safety between older and younger patients in either 4S or HPS.

Because advanced age (≥ 65 years) is a predisposing factor for myopathy, including rhabdomyolysis, ZOCOR 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, including rhabdomyolysis, compared to patients < 65 years of age. [See *Warnings and Precautions (5.1) and Clinical Pharmacology (12.3).*]

8.6 Renal Impairment

Caution should be exercised when ZOCOR is administered to patients with severe renal impairment. [See *Dosage and Administration (2.6).*]

8.7 Hepatic Impairment

ZOCOR is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels [see *Contraindications (4) and Warnings and Precautions (5.2)*].

10 OVERDOSAGE

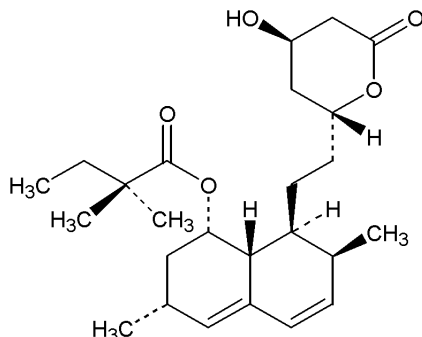
Significant lethality was observed in mice after a single oral dose of 9 g/m². No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m², respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools.

A few cases of overdosage with ZOCOR have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. Supportive measures should be taken in the event of an overdose. The dialyzability of simvastatin and its metabolites in man is not known at present.

11 DESCRIPTION

ZOCOR (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β -hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

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 C₂₅H₃₈O₅ and its molecular weight is 418.57. Its structural formula is:



Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: ascorbic acid, citric acid, hydroxypropyl cellulose,

hypromellose, iron oxides, lactose, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide. Butylated hydroxyanisole is added as a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Simvastatin is a prodrug and is hydrolyzed to its active β -hydroxyacid form, simvastatin acid, after administration. Simvastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces VLDL and TG and increases HDL-C.

12.2 Pharmacodynamics

Epidemiological studies have demonstrated that elevated levels of total-C, LDL-C, as well as decreased levels of HDL-C are associated with the development of atherosclerosis and increased cardiovascular risk. Lowering LDL-C decreases this risk. However, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.3 Pharmacokinetics

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 the 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.

Following an oral dose of ^{14}C -labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. 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. Since simvastatin undergoes extensive first-pass extraction in the liver, the availability of the drug to the general circulation is low (<5%).

Both simvastatin and its β -hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Rat studies indicate that when radiolabeled simvastatin was administered, simvastatin-derived radioactivity crossed the blood-brain barrier.

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. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours postdose. While the recommended therapeutic dose range is 5 to 40 mg/day, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

In a study including 16 elderly patients between 70 and 78 years of age who received ZOCOR 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. Clinical study experience in the elderly (n=1522), suggests that there were no overall differences in safety between elderly and younger patients [see *Use in Specific Populations* (8.5)].

Kinetic studies with another statin, having a similar principal route of elimination, 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).

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of statins. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy [see *Warnings and Precautions* (5.1) and *Drug Interactions* (7.1)].

TABLE 3
Effect of Coadministered Drugs or Grapefruit Juice on Simvastatin Systemic Exposure

Coadministered Drug or Grapefruit Juice	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Simvastatin	Geometric Mean Ratio (Ratio* with / without coadministered drug) No Effect = 1.00		
			AUC	C _{max}	
Contraindicated with simvastatin [see Contraindications (4) and Warnings and Precautions (5.1)]					
Telithromycin [†]	200 mg QD for 4 days	80 mg	simvastatin acid [‡] simvastatin	12 8.9	15 5.3
Nelfinavir [†]	1250 mg BID for 14 days	20 mg QD for 28 days	simvastatin acid [‡] simvastatin	6	6.2
Itraconazole [†]	200 mg QD for 4 days	80 mg	simvastatin acid [‡] simvastatin		13.1 13.1
Posaconazole	100 mg (oral suspension) QD for 13 days	40 mg	simvastatin acid simvastatin	7.3 10.3	9.2 9.4
	200 mg (oral suspension) QD for 13 days	40 mg	simvastatin acid simvastatin	8.5 10.6	9.5 11.4
Gemfibrozil	600 mg BID for 3 days	40 mg	simvastatin acid	2.85	2.18
			simvastatin	1.35	0.91
Avoid >1 quart of grapefruit juice with simvastatin [see Warnings and Precautions (5.1)]					
Grapefruit Juice [§] (high dose)	200 mL of double-strength TID [¶]	60 mg single dose	simvastatin acid simvastatin	7 16	
Grapefruit Juice [§] (low dose)	8 oz (about 237mL) of single-strength [#]	20 mg single dose	simvastatin acid	1.3	
			simvastatin	1.9	
Avoid taking with >10 mg simvastatin , based on clinical and/or post-marketing experience [see Warnings and Precautions (5.1)]					
Verapamil SR	240 mg QD Days 1-7 then 240 mg BID on Days 8-10	80 mg on Day 10	simvastatin acid	2.3	2.4
			simvastatin	2.5	2.1
Diltiazem	120 mg BID for 10 days	80 mg on Day 10	simvastatin acid	2.69	2.69
			simvastatin	3.10	2.88
Diltiazem	120 mg BID for 14 days	20 mg on Day 14	simvastatin	4.6	3.6
Amiodarone	400 mg QD for 3 days	40 mg on Day 3	simvastatin acid	1.75	1.72
			simvastatin	1.76	1.79
Avoid taking with >20 mg simvastatin , based on clinical and/or post-marketing experience [see Warnings and Precautions (5.1)]					
Amlodipine	10 mg QD x 10 days	80 mg on Day 10	simvastatin acid	1.58	1.56
			simvastatin	1.77	1.47
Ranolazine SR	1000 mg BID for 7 days	80 mg on Day 1 and Day 6-9	simvastatin acid simvastatin	2.26 1.86	2.28 1.75
No dosing adjustments required for the following:					
Fenofibrate	160 mg QD X 14 days	80 mg QD on Days 8-14	simvastatin acid	0.64	0.89
			simvastatin	0.89	0.83
Niacin extended-release ^b	2 g single dose	20 mg single dose	simvastatin acid simvastatin	1.6 1.4	1.84 1.08
Propranolol	80 mg single dose	80 mg single dose	total inhibitor	0.79	↓ from 33.6 to 21.1 ng-eq/mL
			active inhibitor	0.79	↓ from 7.0 to 4.7 ng-eq/mL

* Results based on a chemical assay except results with propranolol as indicated.

† Results could be representative of the following CYP3A4 inhibitors: ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, and nefazodone.

‡ Simvastatin acid refers to the β-hydroxyacid of simvastatin.

§ The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.

¶ Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose simvastatin and 30 and 90 minutes following single dose simvastatin on Day 3.

Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and simvastatin was administered in the evening on Day 3.

^b Because Chinese patients have an increased risk for myopathy with simvastatin coadministered with lipid-modifying doses (≥ 1 gram/day niacin) of niacin-containing products, and the risk is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products [see Warnings and Precautions (5.1) and Drug Interactions (7.4)].

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.

Coadministration of simvastatin (40 mg QD for 10 days) resulted in an increase in the maximum mean levels of cardioactive digoxin (given as a single 0.4 mg dose on day 10) by approximately 0.3 ng/mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other statins. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m²), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

13.2 Animal Toxicology and/or Pharmacology

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

14 CLINICAL STUDIES

14.1 Clinical Studies in Adults

Reductions in Risk of CHD Mortality and Cardiovascular Events

In 4S, the effect of therapy with ZOCOR on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with standard care, including diet, and either ZOCOR 20-40 mg/day (n=2,221) or placebo (n=2,223) for a median duration of 5.4 years. Over the course of the study, treatment with ZOCOR led to mean reductions in total-C, LDL-C and TG of 25%, 35%, and 10%, respectively, and a mean increase in HDL-C of 8%. ZOCOR significantly reduced the risk of mortality by 30% (p=0.0003, 182 deaths in the ZOCOR group vs 256 deaths in the placebo group). The risk of CHD mortality was significantly reduced by 42% (p=0.00001, 111 vs 189 deaths). There was no statistically significant difference between groups in non-cardiovascular mortality. ZOCOR significantly decreased the risk of having major coronary events (CHD mortality plus hospital-verified and silent non-fatal myocardial infarction [MI]) by 34% (p<0.00001, 431 vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. ZOCOR significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (p<0.00001, 252 vs 383 patients). ZOCOR significantly reduced the risk of fatal plus non-fatal cerebrovascular events (combined stroke and transient ischemic attacks) by 28% (p=0.033, 75 vs 102 patients). ZOCOR reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels. Because there were only 53 female deaths, the effect of ZOCOR on mortality in women could not be adequately assessed. However, ZOCOR significantly lessened the risk of having major coronary events by 34% (60 vs 91 women with one or more event). The randomization was stratified by angina alone (21% of each treatment group) or a previous MI. Because there were only 57 deaths among the patients with angina alone at baseline, the effect of ZOCOR on mortality in this subgroup could not be adequately assessed. However, trends in reduced coronary mortality, major coronary events and revascularization procedures were consistent between this group and the total study cohort. Additionally, ZOCOR resulted in similar decreases in relative risk for total mortality, CHD mortality, and major coronary events in elderly patients (≥65 years), compared with younger patients.

The Heart Protection Study (HPS) was a large, multi-center, placebo-controlled, double-blind study with a mean duration of 5 years conducted in 20,536 patients (10,269 on ZOCOR 40 mg and 10,267 on placebo). Patients were allocated to treatment using a covariate adaptive method⁴ which took into account the distribution of 10 important baseline characteristics of patients already enrolled and

⁴ D.R. Taves, Minimization: a new method of assigning patients to treatment and control groups. Clin. Pharmacol. Ther. 15 (1974), pp. 443-453

minimized the imbalance of those characteristics across the groups. Patients had a mean age of 64 years (range 40-80 years), were 97% Caucasian and were at high risk of developing a major coronary event because of existing CHD (65%), diabetes (Type 2, 26%; Type 1, 3%), history of stroke or other cerebrovascular disease (16%), peripheral vessel disease (33%), or hypertension in males ≥ 65 years (6%). At baseline, 3,421 patients (17%) had LDL-C levels below 100 mg/dL, of whom 953 (5%) had LDL-C levels below 80 mg/dL; 7,068 patients (34%) had levels between 100 and 130 mg/dL; and 10,047 patients (49%) had levels greater than 130 mg/dL.

The HPS results showed that ZOCOR 40 mg/day significantly reduced: total and CHD mortality; non-fatal MI, stroke, and revascularization procedures (coronary and non-coronary) (see Table 4).

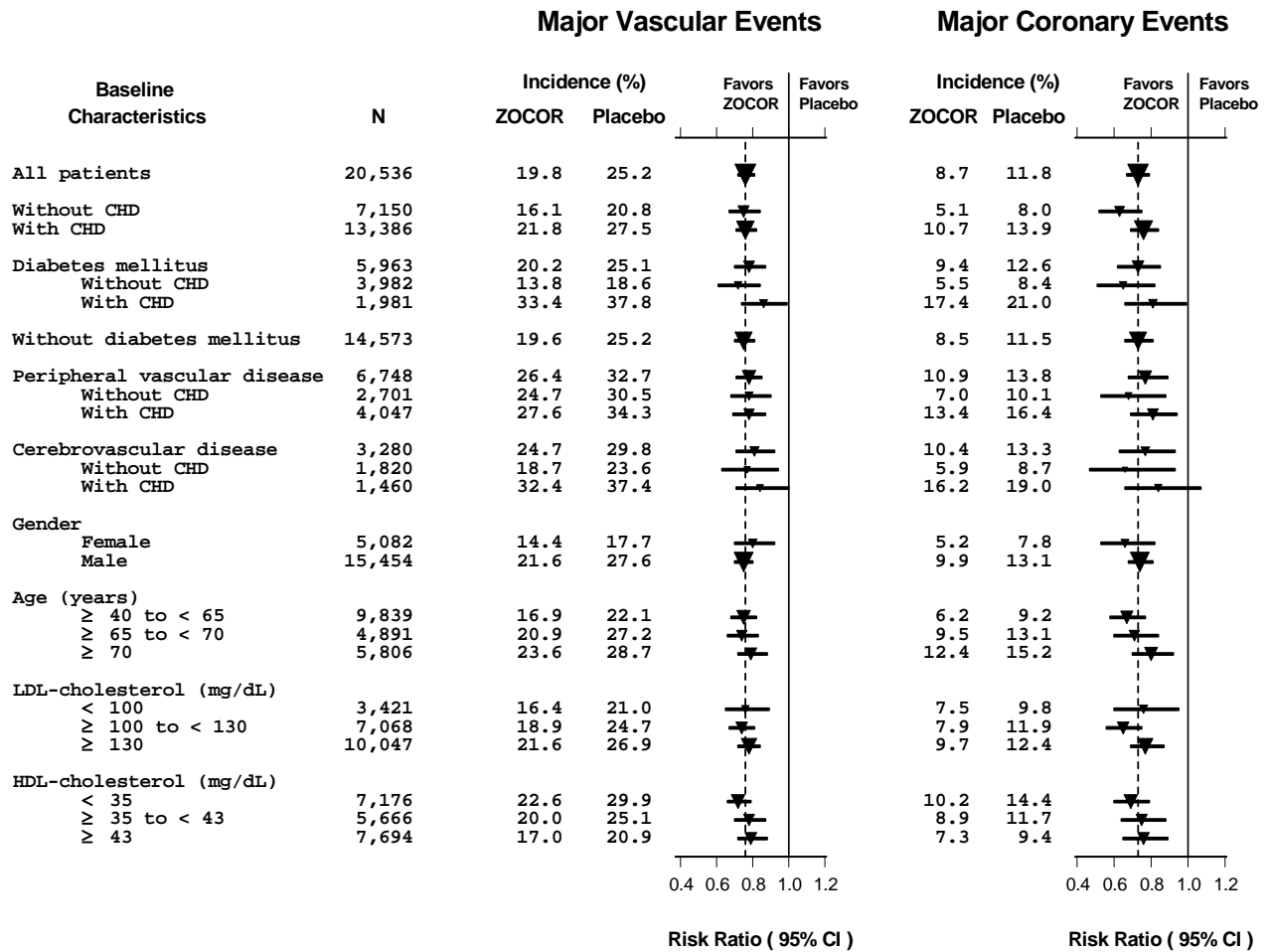
TABLE 4
Summary of Heart Protection Study Results

Endpoint	ZOCOR (N=10,269) n (%) [†]	Placebo (N=10,267) n (%) [†]	Risk Reduction (%) (95% CI)	p-Value
Primary				
Mortality	1,328 (12.9)	1,507 (14.7)	13 (6-19)	p=0.0003
CHD mortality	587 (5.7)	707 (6.9)	18 (8-26)	p=0.0005
Secondary				
Non-fatal MI	357 (3.5)	574 (5.6)	38 (30-46)	p<0.0001
Stroke	444 (4.3)	585 (5.7)	25 (15-34)	p<0.0001
Tertiary				
Coronary revascularization	513 (5)	725 (7.1)	30 (22-38)	p<0.0001
Peripheral and other non-coronary revascularization	450 (4.4)	532 (5.2)	16 (5-26)	p=0.006

[†] n = number of patients with indicated event

Two composite endpoints were defined in order to have sufficient events to assess relative risk reductions across a range of baseline characteristics (see Figure 1). A composite of major coronary events (MCE) was comprised of CHD mortality and non-fatal MI (analyzed by time-to-first event; 898 patients treated with ZOCOR had events and 1,212 patients on placebo had events). A composite of major vascular events (MVE) was comprised of MCE, stroke and revascularization procedures including coronary, peripheral and other non-coronary procedures (analyzed by time-to-first event; 2,033 patients treated with ZOCOR had events and 2,585 patients on placebo had events). Significant relative risk reductions were observed for both composite endpoints (27% for MCE and 24% for MVE, p<0.0001). Treatment with ZOCOR produced significant relative risk reductions for all components of the composite endpoints. The risk reductions produced by ZOCOR in both MCE and MVE were evident and consistent regardless of cardiovascular disease related medical history at study entry (i.e., CHD alone; or peripheral vascular disease, cerebrovascular disease, diabetes or treated hypertension, with or without CHD), gender, age, creatinine levels up to the entry limit of 2.3 mg/dL, baseline levels of LDL-C, HDL-C, apolipoprotein B and A-1, baseline concomitant cardiovascular medications (i.e., aspirin, beta blockers, or calcium channel blockers), smoking status, alcohol intake, or obesity. Diabetics showed risk reductions for MCE and MVE due to ZOCOR treatment regardless of baseline HbA1c levels or obesity with the greatest effects seen for diabetics without CHD.

Figure 1
The Effects of Treatment with ZOCOR on Major Vascular Events and Major Coronary Events in HPS



N = number of patients in each subgroup. The inverted triangles are point estimates of the relative risk, with their 95% confidence intervals represented as a line. The area of a triangle is proportional to the number of patients with MVE or MCE in the subgroup relative to the number with MVE or MCE, respectively, in the entire study population. The vertical solid line represents a relative risk of one. The vertical dashed line represents the point estimate of relative risk in the entire study population.

Angiographic Studies

In the Multicenter Anti-Atheroma Study, the effect of simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic patients with CHD. In this randomized, double-blind, controlled study, patients were treated with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. The co-primary study endpoints were mean change per-patient in minimum and mean lumen diameters, indicating focal and diffuse disease, respectively. ZOCOR significantly slowed the progression of lesions as measured in the Year 4 angiogram by both parameters, as well as by change in percent diameter stenosis. In addition, simvastatin significantly decreased the proportion of patients with new lesions and with new total occlusions.

Modifications of Lipid Profiles

Primary Hyperlipidemia (Fredrickson type IIa and IIb)

ZOCOR has been shown to be effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of hyperlipidemia and in mixed hyperlipidemia. Maximal to near maximal response is generally achieved within 4-6 weeks and maintained during chronic therapy. ZOCOR consistently and

significantly decreased total-C, LDL-C, total-C/HDL-C ratio, and LDL-C/HDL-C ratio; ZOCOR also decreased TG and increased HDL-C (see Table 5).

TABLE 5
Mean Response in Patients with Primary Hyperlipidemia and Combined (mixed) Hyperlipidemia
(Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	TG [†]
<u>Lower Dose Comparative Study</u> [‡] (Mean % Change at Week 6)					
ZOCOR 5 mg q.p.m.	109	-19	-26	10	-12
ZOCOR 10 mg q.p.m.	110	-23	-30	12	-15
<u>Scandinavian Simvastatin Survival Study</u> [§] (Mean % Change at Week 6)					
Placebo	2223	-1	-1	0	-2
ZOCOR 20 mg q.p.m.	2221	-28	-38	8	-19
<u>Upper Dose Comparative Study</u> (Mean % Change Averaged at Weeks 18 and 24)					
ZOCOR 40 mg q.p.m.	433	-31	-41	9	-18
ZOCOR 80 mg q.p.m. [¶]	664	-36	-47	8	-24
<u>Multi-Center Combined Hyperlipidemia Study</u> ^{††} (Mean % Change at Week 6)					
Placebo	125	1	2	3	-4
ZOCOR 40 mg q.p.m.	123	-25	-29	13	-28
ZOCOR 80 mg q.p.m.	124	-31	-36	16	-33

[†] median percent change

[‡] mean baseline LDL-C 244 mg/dL and median baseline TG 168 mg/dL

[§] mean baseline LDL-C 188 mg/dL and median baseline TG 128 mg/dL

^{||} mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

[¶] 21% and 36% median reduction in TG in patients with TG ≤200 mg/dL and TG >200 mg/dL, respectively. Patients with TG >350 mg/dL were excluded

^{††} mean baseline LDL-C 156 mg/dL and median baseline TG 391 mg/dL.

Hypertriglyceridemia (Fredrickson type IV)

The results of a subgroup analysis in 74 patients with type IV hyperlipidemia from a 130-patient, double-blind, placebo-controlled, 3-period crossover study are presented in Table 6.

TABLE 6
Six-week, Lipid-lowering Effects of Simvastatin in Type IV Hyperlipidemia
Median Percent Change (25th and 75th percentile) from Baseline[†]

TREATMENT	N	Total-C	LDL-C	HDL-C	TG	VLDL-C	Non-HDL-C
Placebo	74	+2 (-7, +7)	+1 (-8, +14)	+3 (-3, +10)	-9 (-25, +13)	-7 (-25, +11)	+1 (-9, +8)
ZOCOR 40 mg/day	74	-25 (-34, -19)	-28 (-40, -17)	+11 (+5, +23)	-29 (-43, -16)	-37 (-54, -23)	-32 (-42, -23)
ZOCOR 80 mg/day	74	-32 (-38, -24)	-37 (-46, -26)	+15 (+5, +23)	-34 (-45, -18)	-41 (-57, -28)	-38 (-49, -32)

[†] The median baseline values (mg/dL) for the patients in this study were: total-C = 254, LDL-C = 135, HDL-C = 36, TG = 404, VLDL-C = 83, and non-HDL-C = 215.

Dysbetalipoproteinemia (Fredrickson type III)

The results of a subgroup analysis in 7 patients with type III hyperlipidemia (dysbetalipoproteinemia) (apo E2/2) (VLDL-C/TG>0.25) from a 130-patient, double-blind, placebo-controlled, 3-period crossover study are presented in Table 7.

TABLE 7
Six-week, Lipid-lowering Effects of Simvastatin in Type III Hyperlipidemia
Median Percent Change (min, max) from Baseline[†]

TREATMENT	N	Total-C	LDL-C + IDL	HDL-C	TG	VLDL-C + IDL	Non-HDL-C
Placebo	7	-8 (-24, +34)	-8 (-27, +23)	-2 (-21, +16)	+4 (-22, +90)	-4 (-28, +78)	-8 (-26, -39)
ZOCOR 40 mg/day	7	-50 (-66, -39)	-50 (-60, -31)	+7 (-8, +23)	-41 (-74, -16)	-58 (-90, -37)	-57 (-72, -44)
ZOCOR 80 mg/day	7	-52 (-55, -41)	-51 (-57, -28)	+7 (-5, +29)	-38 (-58, +2)	-60 (-72, -39)	-59 (-61, -46)

[†] The median baseline values (mg/dL) were: total-C = 324, LDL-C = 121, HDL-C = 31, TG = 411, VLDL-C = 170, and non-HDL-C = 291.

Homozygous Familial Hypercholesterolemia

In a controlled clinical study, 12 patients 15-39 years of age with homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses, or 80 mg/day in 3 divided doses. In 11 patients with reductions in LDL-C, the mean LDL-C changes for the 40- and 80-mg doses were 14% (range 8% to 23%, median 12%) and 30% (range 14% to 46%, median 29%), respectively. One patient had an increase of 15% in LDL-C. Another patient with absent LDL-C receptor function had an LDL-C reduction of 41% with the 80-mg dose.

Endocrine Function

In clinical studies, simvastatin did not impair adrenal reserve or significantly reduce basal plasma cortisol concentration. Small reductions from baseline in basal plasma testosterone in men were observed in clinical studies with simvastatin, an effect also observed with other statins and the bile acid sequestrant cholestyramine. There was no effect on plasma gonadotropin levels. In a placebo-controlled, 12-week study there was no significant effect of simvastatin 80 mg on the plasma testosterone response to human chorionic gonadotropin. In another 24-week study, simvastatin 20-40 mg had no detectable effect on spermatogenesis. In 4S, in which 4,444 patients were randomized to simvastatin 20-40 mg/day or placebo for a median duration of 5.4 years, the incidence of male sexual adverse events in the two treatment groups was not significantly different. Because of these factors, the small changes in plasma testosterone are unlikely to be clinically significant. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

14.2 Clinical Studies in Adolescents

In a double-blind, placebo-controlled study, 175 patients (99 adolescent boys and 76 post-menarchal girls) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (HeFH) were randomized to simvastatin (n=106) or placebo (n=67) for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy with simvastatin 40 mg or placebo.

ZOCOR significantly decreased plasma levels of total-C, LDL-C, and Apo B (see Table 8). Results from the extension at 48 weeks were comparable to those observed in the base study.

TABLE 8
Lipid-Lowering Effects of Simvastatin in Adolescent Patients with Heterozygous Familial Hypercholesterolemia
(Mean Percent Change from Baseline)

Dosage	Duration	N		Total-C	LDL-C	HDL-C	TG [†]	Apo B
Placebo	24 Weeks	67	% Change from Baseline (95% CI)	1.6 (-2.2, 5.3)	1.1 (-3.4, 5.5)	3.6 (-0.7, 8.0)	-3.2 (-11.8, 5.4)	-0.5 (-4.7, 3.6)
			Mean baseline, mg/dL (SD)	278.6 (51.8)	211.9 (49.0)	46.9 (11.9)	90.0 (50.7)	186.3 (38.1)
ZOCOR	24 Weeks	106	% Change from Baseline (95% CI)	-26.5 (-29.6, -23.3)	-36.8 (-40.5, -33.0)	8.3 (4.6, 11.9)	-7.9 (-15.8, 0.0)	-32.4 (-35.9, -29.0)
			Mean baseline, mg/dL (SD)	270.2 (44.0)	203.8 (41.5)	47.7 (9.0)	78.3 (46.0)	179.9 (33.8)

[†] median percent change

After 24 weeks of treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the ZOCOR 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

The safety and efficacy of doses above 40 mg daily have not been studied in children with HeFH. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 8360 — Tablets ZOCOR 5 mg are buff, oval, film-coated tablets, coded MSD 726 on one side and ZOCOR 5 on the other. They are supplied as follows:

NDC 0006-0726-31 unit of use bottles of 30

NDC 0006-0726-54 unit of use bottles of 90.

No. 8146 — Tablets ZOCOR 10 mg are peach, oval, film-coated tablets, coded MSD 735 on one side and plain on the other. They are supplied as follows:

NDC 0006-0735-31 unit of use bottles of 30

NDC 0006-0735-54 unit of use bottles of 90

NDC 0006-0735-82 bottles of 1000.

No. 8147 — Tablets ZOCOR 20 mg are tan, oval, film-coated tablets, coded MSD 740 on one side and plain on the other. They are supplied as follows:

NDC 0006-0740-31 unit of use bottles of 30

NDC 0006-0740-54 unit of use bottles of 90

NDC 0006-0740-82 bottles of 1000.

No. 8148 — Tablets ZOCOR 40 mg are brick red, oval, film-coated tablets, coded MSD 749 on one side and plain on the other. They are supplied as follows:

NDC 0006-0749-31 unit of use bottles of 30

NDC 0006-0749-54 unit of use bottles of 90

NDC 0006-0749-82 bottles of 1000.

No. 6577 — Tablets ZOCOR 80 mg are brick red, capsule-shaped, film-coated tablets, coded 543 on one side and 80 on the other. They are supplied as follows:

NDC 0006-0543-31 unit of use bottles of 30

NDC 0006-0543-54 unit of use bottles of 90

NDC 0006-0543-28 unit dose packages of 100

NDC 0006-0543-82 bottles of 1000.

Storage

Store between 5-30°C (41-86°F).

Storage of 1,000 count bottles

Dispense in a tightly-closed container.

17 PATIENT COUNSELING INFORMATION

Patients should be advised to adhere to their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program, and periodic testing of a fasting lipid panel.

Patients should be advised about substances they should not take concomitantly with simvastatin [see Contraindications (4) and Warnings and Precautions (5.1)]. Patients should also be advised to inform other healthcare professionals prescribing a new medication or increasing the dose of an existing medication that they are taking ZOCOR.

17.1 Muscle Pain

All patients starting therapy with ZOCOR should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness. **Patients using the 80-mg dose should be informed that the risk of myopathy, including rhabdomyolysis, is increased with use of the 80-mg dose.** The risk of myopathy, including rhabdomyolysis, occurring with use of ZOCOR is increased when taking certain types of medication or consuming larger quantities of grapefruit juice. Patients should discuss all medication, both prescription and over the counter, with their healthcare professional.

17.2 Liver Enzymes

It is recommended that liver function tests be performed before the initiation of ZOCOR, and thereafter when clinically indicated.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using ZOCOR. Discuss future pregnancy plans with your patients, and discuss when to stop taking ZOCOR if they are trying to conceive. Patients should be advised that if they become pregnant they should stop taking ZOCOR and call their healthcare professional.

17.4 Breastfeeding

Women who are breastfeeding should not use ZOCOR. Patients who have a lipid disorder and are breastfeeding should be advised to discuss the options with their healthcare professional.

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
 **MERCK & CO., INC., Whitehouse Station, NJ 08889, USA**

By:
MERCK SHARP & DOHME LTD.
Cramlington, Northumberland, UK NE23 3JU

Issued June 2011

9992856

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VYTORIN safely and effectively. See full prescribing information for VYTORIN.

VYTORIN (ezetimibe/simvastatin) Tablets

Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Dosage and Administration	
Recommended Dosing (2.1)	06/2011
Restricted Dosing for 10/80 mg (2.2)	06/2011
Coadministration with Other Drugs (2.3)	06/2011
Patients with Homozygous Familial Hypercholesterolemia (2.4)	06/2011
Chinese Patients Taking Lipid-Modifying Doses (≥ 1 g/day Niacin) of Niacin-Containing Products (2.8)	06/2011
Contraindications (4)	06/2011
Warnings and Precautions	
Myopathy/Rhabdomyolysis (5.1)	06/2011
Liver Enzymes (5.2)	06/2011

INDICATIONS AND USAGE

VYTORIN[®], which contains a cholesterol absorption inhibitor and an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet to:

- reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia. (1.1)
- reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments. (1.2)

Limitations of Use (1.3)

- No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.
- VYTORIN has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias.

DOSAGE AND ADMINISTRATION

- Dose range is 10/10 mg/day to 10/40 mg/day. (2.1)
- Recommended usual starting dose is 10/10 or 10/20 mg/day. (2.1)
- Due to the increased risk of myopathy, including rhabdomyolysis, use of the 10/80-mg dose of VYTORIN should be restricted to patients who have been taking VYTORIN 10/80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. (2.2)
- Patients who are currently tolerating the 10/80-mg dose of VYTORIN who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin or statin-based regimen with less potential for the drug-drug interaction. (2.2)
- Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 10/80-mg dose of VYTORIN, patients unable to achieve their LDL-C goal utilizing the 10/40-mg dose of VYTORIN should not be titrated to the 10/80-mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering. (2.2)
- Dosing of VYTORIN should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant. (2.3, 7.5)

DOSAGE FORMS AND STRENGTHS

- Tablets (ezetimibe mg/simvastatin mg): 10/10, 10/20, 10/40, 10/80 (3)

CONTRAINDICATIONS

- Concomitant administration of strong CYP3A4 inhibitors. (4, 5.1)
- Concomitant administration of gemfibrozil, cyclosporine, or danazol. (4, 5.1)
- Hypersensitivity to any component of this medication (4, 6.2)

- Active liver disease or unexplained persistent elevations of hepatic transaminase levels (4, 5.2)
- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)

WARNINGS AND PRECAUTIONS

- **Patients should be advised of the increased risk of myopathy, including rhabdomyolysis, with the 10/80-mg dose. (5.1)**
- Patients should be advised to report promptly any symptoms of myopathy. VYTORIN should be discontinued immediately if myopathy is diagnosed or suspected. (5.1)
- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain medicines. Predisposing factors include advanced age (≥ 65), female gender, uncontrolled hypothyroidism, and renal impairment. (5.1, 8.5, 8.6)
- Liver enzyme abnormalities and monitoring: Persistent elevations in hepatic transaminase can occur. Monitor liver enzymes before and during treatment. (5.2)
- VYTORIN is not recommended in patients with moderate or severe hepatic impairment. (5.3, 12.3)

ADVERSE REACTIONS

- Common (incidence $\geq 2\%$ and greater than placebo) adverse reactions in clinical trials: headache, increased ALT, myalgia, upper respiratory tract infection, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck/Schering-Plough Pharmaceuticals at 1-866-637-2501 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.3, 5.1, 7.1, 7.2, 7.3, 7.6, 7.8)

Interacting Agents	Prescribing Recommendations
Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol	Contraindicated with VYTORIN
Amiodarone, verapamil, diltiazem	Do not exceed 10/10 mg VYTORIN daily
Amlodipine, ranolazine	Do not exceed 10/20 mg VYTORIN daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

- Coumarin anticoagulants: simvastatin prolongs INR. Achieve stable INR prior to starting VYTORIN. Monitor INR frequently until stable upon initiation or alteration of VYTORIN therapy. (7.8)
- Cholestyramine: Combination decreases exposure of ezetimibe. (2.3, 7.5)

USE IN SPECIFIC POPULATIONS

- Severe renal impairment: Caution should be exercised and the patient should be closely monitored. (2.6, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2011

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FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE**

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate.

1.1 Primary Hyperlipidemia

VYTORIN is indicated 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) hyperlipidemia or mixed hyperlipidemia.

1.2 Homozygous Familial Hypercholesterolemia (HoFH)

VYTORIN is indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

1.3 Limitations of Use

No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

VYTORIN has not been studied in Fredrickson type I, III, IV, and V dyslipidemias.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The usual dosage range is 10/10 mg/day to 10/40 mg/day. The recommended usual starting dose is 10/10 mg/day or 10/20 mg/day. VYTORIN should be taken as a single daily dose in the evening, with or without food. 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.

2.2 Restricted Dosing for 10/80 mg

Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 10/80-mg dose of VYTORIN should be restricted to patients who have been taking VYTORIN 10/80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity [see *Warnings and Precautions* (5.1)].

Patients who are currently tolerating the 10/80-mg dose of VYTORIN who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin or statin-based regimen with less potential for the drug-drug interaction.

Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 10/80-mg dose of VYTORIN, patients unable to achieve their LDL-C goal utilizing the 10/40-mg dose of VYTORIN should not be titrated to the 10/80-mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering.

2.3 Coadministration with Other Drugs

Patients taking Amiodarone, Verapamil, or Diltiazem

- The dose of VYTORIN should not exceed 10/10 mg/day [see *Warnings and Precautions* (5.1), *Drug Interactions* (7.3), and *Clinical Pharmacology* (12.3)].

Patients taking Amlodipine or Ranolazine

- The dose of VYTORIN should not exceed 10/20 mg/day [see *Warnings and Precautions* (5.1), *Drug Interactions* (7.3), and *Clinical Pharmacology* (12.3)].

Patients taking Bile Acid Sequestrants

- Dosing of VYTORIN should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant [see *Drug Interactions* (7.5)].

2.4 Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage for patients with homozygous familial hypercholesterolemia is VYTORIN 10/40 mg/day in the evening [see *Dosage and Administration, Restricted Dosing for 10/80 mg* (2.2)]. 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.

2.5 Patients with Hepatic Impairment

No dosage adjustment is necessary in patients with mild hepatic impairment [see *Warnings and Precautions* (5.3)].

2.6 Patients with Renal Impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment. However, for patients with severe renal insufficiency, VYTORIN should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 5 mg or higher. Caution should be exercised when VYTORIN is administered to these patients, and they should be closely monitored [see *Warnings and Precautions* (5.1); *Clinical Pharmacology* (12.3)].

2.7 Geriatric Patients

No dosage adjustment is necessary in geriatric patients [see *Clinical Pharmacology* (12.3)].

2.8 Chinese Patients Taking Lipid-Modifying Doses (≥ 1 g/day Niacin) of Niacin-Containing Products

Because of an increased risk for myopathy in Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products, caution should be used when treating Chinese patients with VYTORIN doses exceeding 10/20 mg/day coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive VYTORIN 10/80 mg coadministered with lipid-modifying doses of niacin-containing products. The cause of the increased risk of myopathy is not known. It is also unknown if the risk for myopathy with coadministration of simvastatin with lipid-modifying

doses of niacin-containing products observed in Chinese patients applies to other Asian patients. [See *Warnings and Precautions (5.1)*.]

3 DOSAGE FORMS AND STRENGTHS

- VYTORIN® 10/10, (ezetimibe 10 mg/simvastatin 10 mg tablets) are white to off-white capsule-shaped tablets with code “311” on one side.
- VYTORIN® 10/20, (ezetimibe 10 mg/simvastatin 20 mg tablets) are white to off-white capsule-shaped tablets with code “312” on one side.
- VYTORIN® 10/40, (ezetimibe 10 mg/simvastatin 40 mg tablets) are white to off-white capsule-shaped tablets with code “313” on one side.
- VYTORIN® 10/80, (ezetimibe 10 mg/simvastatin 80 mg tablets) are white to off-white capsule-shaped tablets with code “315” on one side.

4 CONTRAINDICATIONS

VYTORIN is contraindicated in the following conditions:

- Concomitant administration of strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) [see *Warnings and Precautions (5.1)*].
- Concomitant administration of gemfibrozil, cyclosporine, or danazol [see *Warnings and Precautions (5.1)*].
- Hypersensitivity to any component of this medication [see *Adverse Reactions (6.2)*].
- Active liver disease or unexplained persistent elevations in hepatic transaminase levels [see *Warnings and Precautions (5.2)*].
- Women who are pregnant or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because HMG-CoA reductase inhibitors (statins), such as simvastatin, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, VYTORIN may cause fetal harm when administered to a pregnant woman. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of VYTORIN use during pregnancy; however, in rare reports congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, simvastatin revealed no evidence of teratogenicity. **VYTORIN should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, VYTORIN should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].
- Nursing mothers. It is not known whether simvastatin is excreted into human milk; however, a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require VYTORIN treatment should not breast-feed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy/Rhabdomyolysis

Simvastatin occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase above ten times 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 risk of myopathy is increased by high levels of statin activity in plasma. Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

The risk of myopathy, including rhabdomyolysis, is dose related. 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% and 0.08% at 20 and 40 mg/day, respectively. The incidence of myopathy with 80 mg (0.61%) was disproportionately higher than that observed at the lower doses. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which 12,064 patients with a history of myocardial infarction were treated with simvastatin (mean follow-up 6.7 years), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] >10 times upper limit of normal [ULN]) in patients on 80 mg/day was approximately 0.9% compared with 0.02% for patients on 20 mg/day. The incidence of rhabdomyolysis (defined as myopathy with a CK >40 times ULN) in patients on 80 mg/day was approximately 0.4% compared with 0% for patients on 20 mg/day. The incidence of myopathy, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent years of treatment. In this trial, patients were carefully monitored and some interacting medicinal products were excluded.

The risk of myopathy, including rhabdomyolysis, is greater in patients on simvastatin 80 mg compared with other statin therapies with similar or greater LDL-C-lowering efficacy and compared with lower doses of simvastatin. Therefore, the 10/80-mg dose of VYTORIN should be used only in patients who have been taking VYTORIN 10/80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity [see Dosage and Administration, Restricted Dosing for 10/80 mg (2.2)]. If, however, a patient who is currently tolerating the 10/80-mg dose of VYTORIN needs to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin, that patient should be switched to an alternative statin or statin-based regimen with less potential for the drug-drug interaction. Patients should be advised of the increased risk of myopathy, including rhabdomyolysis, and to report promptly any unexplained muscle pain, tenderness or weakness. If symptoms occur, treatment should be discontinued immediately [see Warnings and Precautions (5.2)].

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin prior to initiating ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to agents known to be associated with increased risk of rhabdomyolysis, such as fibrates.

All patients starting therapy with VYTORIN or whose dose of VYTORIN is being increased should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness. VYTORIN therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when simvastatin treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients taking VYTORIN merit closer monitoring. Therapy with VYTORIN should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Drug Interactions

The risk of myopathy and rhabdomyolysis is increased by high levels of statin activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs that inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily). Combination of these drugs with VYTORIN is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with VYTORIN must be suspended during the course of treatment. [See Contraindications (4) and Drug Interactions (7).] *In vitro* studies have demonstrated a potential for voriconazole to inhibit the metabolism of simvastatin. Adjustment of the VYTORIN dose may be needed to reduce the risk of myopathy/rhabdomyolysis if voriconazole must be used concomitantly with VYTORIN. [See Drug Interactions (7.1).]

The combined use of VYTORIN with gemfibrozil, cyclosporine, or danazol is contraindicated [see *Contraindications (4) and Drug Interactions (7.1 and 7.2)*].

Caution should be used when prescribing other fibrates with VYTORIN, as these agents can cause myopathy when given alone and the risk is increased when they are co-administered [see *Drug Interactions (7.2, 7.7)*].

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing VYTORIN with colchicine [see *Drug Interactions (7.9)*].

The benefits of the combined use of VYTORIN with the following drugs should be carefully weighed against the potential risks of combinations: other lipid-lowering drugs (other fibrates or ≥ 1 g/day of niacin), amiodarone, verapamil, diltiazem, amlodipine, or ranolazine [see *Drug Interactions (7.3) and Table 6 in Clinical Pharmacology (12.3)*].

Cases of myopathy, including rhabdomyolysis, have been observed with simvastatin coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products. In an ongoing, double-blind, randomized cardiovascular outcomes trial, an independent safety monitoring committee identified that the incidence of myopathy is higher in Chinese compared with non-Chinese patients taking simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg coadministered with lipid-modifying doses of a niacin-containing product. Caution should be used when treating Chinese patients with VYTORIN in doses exceeding 10/20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive VYTORIN 10/80 mg coadministered with lipid-modifying doses of niacin-containing products. It is unknown if the risk for myopathy with coadministration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients [see *Drug Interactions (7.4)*].

Prescribing recommendations for interacting agents are summarized in Table 1 [see also *Dosage and Administration (2.3), Drug Interactions (7), and Clinical Pharmacology (12.3)*].

Table 1
Drug Interactions Associated with Increased
Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone Gemfibrozil Cyclosporine Danazol	Contraindicated with VYTORIN
Amiodarone Verapamil Diltiazem	Do not exceed 10/10 mg VYTORIN daily
Amlodipine Ranolazine	Do not exceed 10/20 mg VYTORIN daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

5.2 Liver Enzymes

In three placebo-controlled, 12-week trials, the incidence of consecutive elevations (≥ 3 X ULN) in serum transaminases was 1.7% overall for patients treated with VYTORIN and appeared to be dose-related with an incidence of 2.6% for patients treated with VYTORIN 10/80. In controlled long-term (48-week) extensions, which included both newly-treated and previously-treated patients, the incidence of consecutive elevations (≥ 3 X ULN) in serum transaminases was 1.8% overall and 3.6% for patients treated with VYTORIN 10/80. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

It is recommended that liver function tests be performed before the initiation of treatment with VYTORIN, and thereafter when clinically indicated. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed

thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 X ULN or greater persist, withdrawal of therapy with VYTORIN is recommended. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy [see *Warnings and Precautions* (5.1)].

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.

5.3 Hepatic Impairment

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, VYTORIN is not recommended in these patients. [See *Clinical Pharmacology* (12.3).]

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Rhabdomyolysis and myopathy [see *Warnings and Precautions* (5.1)]
- Liver enzyme abnormalities [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

VYTORIN

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In the VYTORIN (ezetimibe/simvastatin) placebo-controlled clinical trials database of 1420 patients (age range 20-83 years, 52% women, 87% Caucasians, 3% Blacks, 5% Hispanics, 3% Asians) with a median treatment duration of 27 weeks, 5% of patients on VYTORIN and 2.2% of patients on placebo discontinued due to adverse reactions.

The most common adverse reactions in the group treated with VYTORIN that led to treatment discontinuation and occurred at a rate greater than placebo were:

- Increased ALT (0.9%)
- Myalgia (0.6%)
- Increased AST (0.4%)
- Back pain (0.4%)

The most commonly reported adverse reactions (incidence $\geq 2\%$ and greater than placebo) in controlled clinical trials were: headache (5.8%), increased ALT (3.7%), myalgia (3.6%), upper respiratory tract infection (3.6%), and diarrhea (2.8%).

VYTORIN has been evaluated for safety in more than 10,189 patients in clinical trials.

Table 2 summarizes the frequency of clinical adverse reactions reported in $\geq 2\%$ of patients treated with VYTORIN (n=1420) and at an incidence greater than placebo, regardless of causality assessment, from four placebo-controlled trials.

Table 2*
Clinical Adverse Reactions Occurring in ≥2% of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Reaction	Placebo (%) n=371	Ezetimibe 10 mg (%) n=302	Simvastatin** (%) n=1234	VYTORIN** (%) n=1420
<i>Body as a whole – general disorders</i>				
Headache	5.4	6.0	5.9	5.8
<i>Gastrointestinal system disorders</i>				
Diarrhea	2.2	5.0	3.7	2.8
<i>Infections and infestations</i>				
Influenza	0.8	1.0	1.9	2.3
Upper respiratory tract infection	2.7	5.0	5.0	3.6
<i>Musculoskeletal and connective tissue disorders</i>				
Myalgia	2.4	2.3	2.6	3.6
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 coadministered and two placebo-controlled studies in which VYTORIN was administered.

**All doses.

Ezetimibe

Other adverse reactions reported with ezetimibe in placebo-controlled studies, regardless of causality assessment: *Musculoskeletal system disorders*: arthralgia; *Infections and infestations*: sinusitis; *Body as a whole – general disorders*: fatigue.

Simvastatin

In a clinical trial in which 12,064 patients with a history of myocardial infarction were treated with simvastatin (mean follow-up 6.7 years), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] >10 times upper limit of normal [ULN]) in patients on 80 mg/day was approximately 0.9% compared with 0.02% for patients on 20 mg/day. The incidence of rhabdomyolysis (defined as myopathy with a CK >40 times ULN) in patients on 80 mg/day was approximately 0.4% compared with 0% for patients on 20 mg/day. The incidence of myopathy, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent years of treatment. In this trial, patients were carefully monitored and some interacting medicinal products were excluded.

Other adverse reactions reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment: *Cardiac disorders*: atrial fibrillation; *Ear and labyrinth disorders*: vertigo; *Gastrointestinal disorders*: abdominal pain, constipation, dyspepsia, flatulence, gastritis; *Skin and subcutaneous tissue disorders*: eczema, rash; *Endocrine disorders*: diabetes mellitus; *Infections and infestations*: bronchitis, sinusitis, urinary tract infections; *Body as a whole – general disorders*: asthenia, edema/swelling; *Psychiatric disorders*: insomnia.

Laboratory Tests

Marked persistent increases of hepatic serum transaminases have been noted [see *Warnings and Precautions* (5.2)]. Elevated alkaline phosphatase and γ -glutamyl transpeptidase have been reported. About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK [see *Warnings and Precautions* (5.1)].

6.2 Post-Marketing Experience

Because the below reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been reported in post-marketing experience for VYTORIN or ezetimibe or simvastatin: pruritus; alopecia; erythema multiforme; a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails); dizziness; muscle cramps; myalgia; arthralgia; pancreatitis; memory impairment; paresthesia; peripheral neuropathy; vomiting; nausea; anemia; erectile dysfunction; interstitial lung disease; myopathy/rhabdomyolysis [see *Warnings and Precautions* (5.1)]; hepatitis/jaundice; hepatic failure; depression; cholelithiasis; cholecystitis; thrombocytopenia; elevations in liver transaminases; elevated creatine phosphokinase.

Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria have been reported.

In addition, an apparent hypersensitivity syndrome has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

7 DRUG INTERACTIONS

[See *Clinical Pharmacology (12.3)*.]

VYTORIN

7.1 Strong CYP3A4 Inhibitors, cyclosporine or danazol

Strong CYP3A4 inhibitors: The risk of myopathy is increased by reducing the elimination of the simvastatin component of VYTORIN. Hence when VYTORIN is used with an inhibitor of CYP3A4 (e.g., as listed below), elevated plasma levels of HMG-CoA reductase inhibitory activity increases the risk of myopathy and rhabdomyolysis, particularly with higher doses of VYTORIN. [See *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*.] Concomitant use of drugs labeled as having a strong inhibitory effect on CYP3A4 is contraindicated [see *Contraindications (4)*]. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with VYTORIN must be suspended during the course of treatment.

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of simvastatin. It is recommended that dose adjustment of VYTORIN be considered during concomitant use of voriconazole and VYTORIN to reduce the risk of myopathy, including rhabdomyolysis. [see *Warnings and Precautions (5.1)*].

Cyclosporine or Danazol: The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol. Therefore, concomitant use of these drugs is contraindicated. [see *Contraindications (4)*, *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

7.2 Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

Gemfibrozil: Contraindicated with VYTORIN [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].

Other fibrates: Caution should be used when prescribing with VYTORIN [see *Warnings and Precautions (5.1)*].

7.3 Amiodarone, Ranolazine, or Calcium Channel Blockers

The risk of myopathy, including rhabdomyolysis, is increased by concomitant administration of amiodarone, ranolazine, or calcium channel blockers such as verapamil, diltiazem or amlodipine [see *Dosage and Administration (2.3)* and *Warnings and Precautions (5.1)* and *Table 6 in Clinical Pharmacology (12.3)*].

7.4 Niacin

Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products. In particular, caution should be used when treating Chinese patients with VYTORIN doses exceeding 10/20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive VYTORIN 10/80 mg coadministered with lipid-modifying doses of niacin-containing products. [See *Warnings and Precautions (5.1)*].

7.5 Cholestyramine

Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding VYTORIN to cholestyramine may be reduced by this interaction.

7.6 Digoxin

In one study, concomitant administration of digoxin with simvastatin resulted in a slight elevation in plasma digoxin concentrations. Patients taking digoxin should be monitored appropriately when VYTORIN is initiated.

7.7 Fibrates

The safety and effectiveness of VYTORIN administered with fibrates have not been established.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile [see *Animal Toxicology and/or Pharmacology* (13.2)]. Coadministration of VYTORIN with fibrates is not recommended until use in patients is studied. [See *Warnings and Precautions* (5.1).]

7.8 Coumarin Anticoagulants

Simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in a normal volunteer study and in a hypercholesterolemic patient study, respectively. With other statins, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting VYTORIN and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of VYTORIN is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

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

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

7.9 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing VYTORIN with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X.

[See *Contraindications* (4).]

VYTORIN

VYTORIN is contraindicated in women who are or may become pregnant. Lipid-lowering drugs offer no benefit during pregnancy, because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy. There are no adequate and well-controlled studies of VYTORIN use during pregnancy; however, there are rare reports of congenital anomalies in infants exposed to statins *in utero*. Animal reproduction studies of simvastatin in rats and rabbits showed no evidence of teratogenicity. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because statins, such as simvastatin, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, VYTORIN may cause fetal harm when administered to a pregnant woman. If VYTORIN is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Women of childbearing potential, who require VYTORIN treatment for a lipid disorder, should be advised to use effective contraception. For women trying to conceive, discontinuation of VYTORIN should be considered. If pregnancy occurs, VYTORIN should be immediately discontinued.

Ezetimibe

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryo-lethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 times the

human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple-dose studies of ezetimibe coadministered with statins in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in coadministration therapy compared to monotherapy.

Simvastatin

Simvastatin was not teratogenic in rats or rabbits at doses (25, 10 mg/kg/day, respectively) that resulted in 3 times the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related statin, skeletal malformations were observed in rats and mice.

There are rare reports of congenital anomalies following intrauterine exposure to statins. In a review¹ of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally-related statin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

8.3 Nursing Mothers

It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants. A decision should be made whether to discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother [see *Contraindications (4)*].

In rat studies, exposure to ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe or simvastatin are excreted into human breast milk. Because a small amount of another drug in the same class as simvastatin is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women who are nursing should not take VYTORIN [see *Contraindications (4)*].

8.4 Pediatric Use

The effects of ezetimibe coadministered with simvastatin (n=126) compared to simvastatin monotherapy (n=122) have been evaluated in adolescent boys and girls with heterozygous familial hypercholesterolemia (HeFH). In a multicenter, double-blind, controlled study followed by an open-label phase, 142 boys and 106 postmenarchal girls, 10 to 17 years of age (mean age 14.2 years, 43% females, 82% Caucasians, 4% Asian, 2% Blacks, 13% multi-racial) with HeFH were randomized to receive either ezetimibe coadministered with simvastatin or simvastatin monotherapy. Inclusion in the study required 1) a baseline LDL-C level between 160 and 400 mg/dL and 2) a medical history and clinical presentation consistent with HeFH. The mean baseline LDL-C value was 225 mg/dL (range: 161-351 mg/dL) in the ezetimibe coadministered with simvastatin group compared to 219 mg/dL (range: 149-336 mg/dL) in the simvastatin monotherapy group. The patients received coadministered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) or simvastatin monotherapy (10 mg, 20 mg, or 40 mg) for 6 weeks, coadministered ezetimibe and 40 mg simvastatin or 40 mg simvastatin monotherapy for the next 27 weeks, and open-label coadministered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter.

The results of the study at Week 6 are summarized in Table 3. Results at Week 33 were consistent with those at Week 6.

¹ Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy, *Reproductive Toxicology*, 10(6):439-446, 1996.

Table 3
Mean Percent Difference at Week 6 Between the Pooled Ezetimibe Coadministered with Simvastatin Group and the Pooled Simvastatin Monotherapy Group in Adolescent Patients with Heterozygous Familial Hypercholesterolemia

	Total-C	LDL-C	Apo B	Non-HDL-C	TG^a	HDL-C
Mean percent difference between treatment groups	-12%	-15%	-12%	-14%	-2%	+0.1%
95% Confidence Interval	(-15%, -9%)	(-18%, -12%)	(-15%, -9%)	(-17%, -11%)	(-9, +4)	(-3, +3)

^a For triglycerides, median % change from baseline

From the start of the trial to the end of Week 33, discontinuations due to an adverse reaction occurred in 7 (6%) patients in the ezetimibe coadministered with simvastatin group and in 2 (2%) patients in the simvastatin monotherapy group.

During the trial, hepatic transaminase elevations (two consecutive measurements for ALT and/or AST ≥ 3 X ULN) occurred in four (3%) individuals in the ezetimibe coadministered with simvastatin group and in two (2%) individuals in the simvastatin monotherapy group. Elevations of CPK (≥ 10 X ULN) occurred in two (2%) individuals in the ezetimibe coadministered with simvastatin group and in zero individuals in the simvastatin monotherapy group.

In this limited controlled study, there was no significant effect on growth or sexual maturation in the adolescent boys or girls, or on menstrual cycle length in girls.

Coadministration of ezetimibe with simvastatin at doses greater than 40 mg/day has not been studied in adolescents. Also, VYTORIN has not been studied in patients younger than 10 years of age or in premenarchal girls.

Ezetimibe

Based on total ezetimibe (ezetimibe + ezetimibe-glucuronide) there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Simvastatin

The pharmacokinetics of simvastatin has not been studied in the pediatric population.

8.5 Geriatric Use

Of the 10,189 patients who received VYTORIN in clinical studies, 3242 (32%) were 65 and older (this included 844 (8%) who were 75 and older). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients but greater sensitivity of some older individuals cannot be ruled out. Since advanced age (≥ 65 years) is a predisposing factor for myopathy, VYTORIN should be prescribed with caution in the elderly. [See *Clinical Pharmacology (12.3).*]

Because advanced age (≥ 65 years) is a predisposing factor for myopathy, including rhabdomyolysis, 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, including rhabdomyolysis, compared to patients <65 years of age. [See *Warnings and Precautions (5.1) and Clinical Pharmacology (12.3).*]

8.6 Renal Impairment

Caution should be exercised when VYTORIN is administered to patients with severe renal impairment. [See *Dosage and Administration (2.6).*]

8.7 Hepatic Impairment

VYTORIN is contraindicated in patients with active liver disease or unexplained persistent elevations of hepatic transaminases. VYTORIN is not recommended in patients with moderate to severe hepatic impairment. [See *Contraindications (4) and Warnings and Precautions (5.2).*]

10 OVERDOSAGE

VYTORIN

No specific treatment of overdose with VYTORIN can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed.

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hyperlipidemia for up to 56 days, was generally well tolerated.

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

Simvastatin

Significant lethality was observed in mice after a single oral dose of 9 g/m². No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m², respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools.

A few cases of overdosage with simvastatin have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

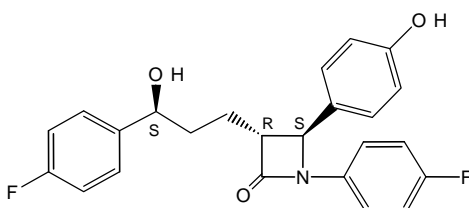
The dialyzability of simvastatin and its metabolites in man is not known at present.

11 DESCRIPTION

VYTORIN contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and simvastatin, an HMG-CoA reductase inhibitor.

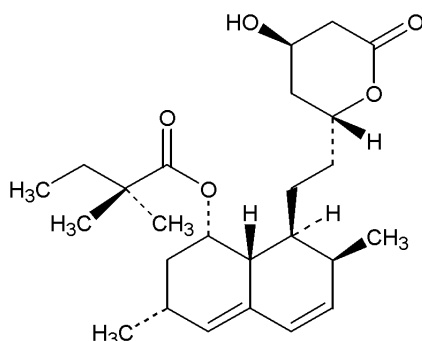
The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is C₂₄H₂₁F₂NO₃ and its molecular weight is 409.4.

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-[1α,3α,7β,8β(2S*,4S*),-8aβ]]. The empirical formula of simvastatin is C₂₅H₃₈O₅ 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, hypromellose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, and propyl gallate NF.

12 CLINICAL PHARMACOLOGY

12.1 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 reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. 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 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 statins [see *Clinical Studies (14)*].

Simvastatin

Simvastatin is a prodrug and is hydrolyzed to its active β -hydroxyacid form, simvastatin acid, after administration. Simvastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces very-low-density lipoproteins (VLDL) and TG and increases HDL-C.

12.2 Pharmacodynamics

Clinical studies have demonstrated that elevated levels of total-C, LDL-C and Apo B, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of 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 VLDL, intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.3 Pharmacokinetics

The results of a bioequivalence study in healthy subjects demonstrated that the VYTORIN (ezetimibe/simvastatin) 10 mg/10 mg to 10 mg/80 mg combination tablets are bioequivalent to coadministration of corresponding doses of ezetimibe (ZETIA®) and simvastatin (ZOCOR®) as individual tablets.

Absorption

Ezetimibe

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide).

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.

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 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.

Following an oral dose of ^{14}C -labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. 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.

Specific 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: [See Pediatric Use (8.4).]

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 Black and Caucasian subjects. Studies in Asian subjects indicated that the pharmacokinetics of ezetimibe was similar to those seen in Caucasian subjects.

Hepatic Impairment

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 impairment (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 impairment, the mean AUC for total ezetimibe and ezetimibe increased approximately 4-fold compared to healthy subjects.

Renal Impairment

Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl \leq 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 impairment (as measured by creatinine clearance).

Drug Interactions [See also Drug Interactions (7).]

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with simvastatin. No specific pharmacokinetic drug interaction studies with VYTORIN have been conducted other than the following study with NIASPAN (Niacin extended-release tablets).

Niacin: The effect of VYTORIN (10/20 mg daily for 7 days) on the pharmacokinetics of NIASPAN extended-release tablets (1000 mg for 2 days and 2000 mg for 5 days following a low-fat breakfast) was studied in healthy subjects. The mean C_{max} and AUC of niacin increased 9% and 22%, respectively. The mean C_{max} and AUC of nicotinic acid increased 10% and 19%, respectively (N=13). In the same study, the effect of NIASPAN on the pharmacokinetics of VYTORIN was evaluated (N=15). While concomitant NIASPAN decreased the mean C_{max} of total ezetimibe (1%), and simvastatin (2%), it increased the mean C_{max} of simvastatin acid (18%). In addition, concomitant NIASPAN increased the mean AUC of total ezetimibe (26%), simvastatin (20%), and simvastatin acid (35%).

Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (\geq 1 g/day niacin) of niacin-containing products. [See Warnings and Precautions (5.1) and Drug Interactions (7.4).]

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.

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of statins. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4.

Simvastatin is a substrate for CYP3A4. Inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy. [See *Warnings and Precautions (5.1); Drug Interactions (7.1).*]

Ezetimibe

Table 4
Effect of Coadministered Drugs on Total Ezetimibe

Coadministered Drug and Dosing Regimen	Total Ezetimibe*	
	Change in AUC	Change in C _{max}
Cyclosporine-stable dose required (75-150 mg BID) ^{†, **}	↑240%	↑290%
Fenofibrate, 200 mg QD, 14 days [†]	↑48%	↑64%
Gemfibrozil, 600 mg BID, 7 days [†]	↑64%	↑91%
Cholestyramine, 4 g BID, 14 days [†]	↓55%	↓4%
Aluminum & magnesium hydroxide combination antacid, single dose [§]	↓4%	↓30%
Cimetidine, 400 mg BID, 7 days	↑6%	↑22%
Glipizide, 10 mg, single dose	↑4%	↓8%
Statins		
Lovastatin 20 mg QD, 7 days	↑9%	↑3%
Pravastatin 20 mg QD, 14 days	↑7%	↑23%
Atorvastatin 10 mg QD, 14 days	↓2%	↑12%
Rosuvastatin 10 mg QD, 14 days	↑13%	↑18%
Fluvastatin 20 mg QD, 14 days	↓19%	↑7%

* Based on 10 mg-dose of ezetimibe

** Post-renal transplant patients with mild impaired or normal renal function. 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.

[†] See 7. Drug Interactions

[§] Supralox[®], 20 mL

Table 5
Effect of Ezetimibe Coadministration on Systemic Exposure to Other Drugs

Coadministered Drug and its Dosage Regimen	Ezetimibe Dosage Regimen	Change in AUC of Coadministered Drug	Change in C _{max} of Coadministered Drug
Warfarin, 25 mg single dose on Day 7	10 mg QD, 11 days	↓2% (R-warfarin)	↑3% (R-warfarin)
		↓4% (S-warfarin)	↑1% (S-warfarin)
Digoxin, 0.5 mg single dose	10 mg QD, 8 days	↑2%	↓7%
Gemfibrozil, 600 mg BID, 7 days [†]	10 mg QD, 7 days	↓1%	↓11%
Ethinyl estradiol & Levonorgestrel, QD, 21 days	10 mg QD, Days 8-14 of 21 day oral contraceptive cycle	Ethinyl estradiol	Ethinyl estradiol
		0%	↓9%
Levonorgestrel	10 mg QD, Days 8-14 of 21 day oral contraceptive cycle	Levonorgestrel	Levonorgestrel
		0%	↓5%
Glipizide, 10 mg on Days 1 and 9	10 mg QD, Days 2-9	↓3%	↓5%
Fenofibrate, 200 mg QD, 14 days [†]	10 mg QD, 14 days	↑11%	↑7%
Cyclosporine, 100 mg single dose Day 7 [†]	20 mg QD, 8 days	↑15%	↑10%
Statins			
Lovastatin 20 mg QD, 7 days	10 mg QD, 7 days	↑19%	↑3%
Pravastatin 20 mg QD, 14 days	10 mg QD, 14 days	↓20%	↓24%
Atorvastatin 10 mg QD, 14 days	10 mg QD, 14 days	↓4%	↑7%
Rosuvastatin 10 mg QD, 14 days	10 mg QD, 14 days	↑19%	↑17%
Fluvastatin 20 mg QD, 14 days	10 mg QD, 14 days	↓39%	↓27%

[†] See 7. Drug Interactions

Simvastatin

Table 6
Effect of Coadministered Drugs or Grapefruit Juice on Simvastatin Systemic Exposure

Coadministered Drug or Grapefruit Juice	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Simvastatin	Geometric Mean Ratio (Ratio* with / without coadministered drug) No Effect = 1.00		
				AUC	C _{max}
Contraindicated with VYTORIN [see Contraindications (4) and Warnings and Precautions (5.1)]					
Telithromycin [†]	200 mg QD for 4 days	80 mg	simvastatin acid [‡]	12	15
			simvastatin	8.9	5.3
Nelfinavir [‡]	1250 mg BID for 14 days	20 mg QD for 28 days	simvastatin acid [‡]		
			simvastatin	6	6.2
Itraconazole [†]	200 mg QD for 4 days	80 mg	simvastatin acid [‡]		13.1
			simvastatin		13.1
Posaconazole	100 mg (oral suspension) QD for 13 days	40 mg	simvastatin acid [‡]	7.3	9.2
			simvastatin	10.3	9.4
	200 mg (oral suspension) QD for 13 days	40 mg	simvastatin acid [‡]	8.5	9.5
			simvastatin	10.6	11.4
Gemfibrozil	600 mg BID for 3 days	40 mg	simvastatin acid [‡]	2.85	2.18
			simvastatin	1.35	0.91
Avoid >1 quart of grapefruit juice with VYTORIN [see Warnings and Precautions (5.1)]					
Grapefruit Juice [§] (high dose)	200 mL of double-strength TID [¶]	60 mg single dose	simvastatin acid	7	
			simvastatin	16	
Grapefruit Juice [§] (low dose)	8 oz (about 237 mL) of single-strength [#]	20 mg single dose	simvastatin acid	1.3	
			simvastatin	1.9	
Avoid taking with >10/10 mg VYTORIN, based on clinical and/or post-marketing simvastatin experience [see Warnings and Precautions (5.1)]					
Verapamil SR	240 mg QD Days 1-7 then 240 mg BID on Days 8-10	80 mg on Day 10	simvastatin acid	2.3	2.4
			simvastatin	2.5	2.1
Diltiazem	120 mg BID for 10 days	80 mg on Day 10	simvastatin acid	2.69	2.69
			simvastatin	3.10	2.88
Diltiazem	120 mg BID for 14 days	20 mg on Day 14	simvastatin	4.6	3.6
Amiodarone	400 mg QD for 3 days	40 mg on Day 3	simvastatin	1.75	1.72
			simvastatin acid	1.76	1.79
Avoid taking with >10/20 mg VYTORIN, based on clinical and/or post-marketing simvastatin experience [see Warnings and Precautions (5.1)]					
Amlodipine	10 mg QD for 10 days	80 mg on Day 10	simvastatin acid	1.58	1.56
			simvastatin	1.77	1.47
Ranolazine SR	1000 mg BID for 7 days	80 mg on Day 1 and Days 6-9	simvastatin acid	2.26	2.28
			simvastatin	1.86	1.75
No dosing adjustments required for the following:					
Fenofibrate	160 mg QD for 14 days	80 mg QD on Days 8-14	simvastatin acid	0.64	0.89
			simvastatin	0.89	0.83
Propranolol	80 mg single dose	80 mg single dose	total inhibitor	0.79	↓ from 33.6 to 21.1 ng-eq/mL
			active inhibitor	0.79	↓ from 7.0 to 4.7 ng-eq/mL

* Results based on a chemical assay except results with propranolol as indicated.

† Results could be representative of the following CYP3A4 inhibitors: ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, and nefazodone.

‡ Simvastatin acid refers to the β-hydroxyacid of simvastatin.

§ The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.

¶ Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose simvastatin and 30 and 90 minutes following single dose simvastatin on Day 3.

Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and simvastatin was administered in the evening on Day 3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

VYTORIN

No animal carcinogenicity or fertility studies have been conducted with the combination of ezetimibe and simvastatin. The combination of ezetimibe with simvastatin did not show evidence of mutagenicity *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with ezetimibe and simvastatin with or without

metabolic activation. There was no evidence of genotoxicity at doses up to 600 mg/kg with the combination of ezetimibe and simvastatin (1:1) in the *in vivo* mouse micronucleus test.

Ezetimibe

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe).

Simvastatin

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively, (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other statins. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80-mg daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m²), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day (approximately

2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

13.2 Animal Toxicology and/or Pharmacology

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels, were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

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 µg/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 µg/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.

In 1-month studies in dogs given ezetimibe (0.03 to 300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14-day study in mice given ezetimibe (0.3 to 5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

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

In 4- to 12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug-metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with statins (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia

VYTORIN

VYTORIN reduces total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C in patients with hyperlipidemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy.

VYTORIN is effective in men and women with hyperlipidemia. Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of VYTORIN.

Five multicenter, double-blind studies conducted with either VYTORIN or coadministered ezetimibe and simvastatin equivalent to VYTORIN in patients with primary hyperlipidemia 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, 1528 hyperlipidemic patients were randomized to one of ten treatment groups: placebo, ezetimibe (10 mg), simvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or VYTORIN (10/10, 10/20, 10/40, or 10/80).

When patients receiving VYTORIN were compared to those receiving all doses of simvastatin, VYTORIN significantly lowered total-C, LDL-C, Apo B, TG, and non-HDL-C. 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 7.) The lipid response to VYTORIN was similar in patients with TG levels greater than or less than 200 mg/dL.

Table 7
Response to VYTORIN in Patients with Primary Hyperlipidemia
(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	609	-38	-53	-42	+7	-24	-49
Pooled data (All simvastatin doses) ^c	622	-28	-39	-32	+7	-21	-36
Ezetimibe 10 mg	149	-13	-19	-15	+5	-11	-18
Placebo	148	-1	-2	0	0	-2	-2
VYTORIN by dose							
10/10	152	-31	-45	-35	+8	-23	-41
10/20	156	-36	-52	-41	+10	-24	-47
10/40	147	-39	-55	-44	+6	-23	-51
10/80	154	-43	-60	-49	+6	-31	-56
Simvastatin by dose							
10 mg	158	-23	-33	-26	+5	-17	-30
20 mg	150	-24	-34	-28	+7	-18	-32
40 mg	156	-29	-41	-33	+8	-21	-38
80 mg	158	-35	-49	-39	+7	-27	-45

^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 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 \geq 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 (see Table 8).

Table 8
Response to VYTORIN after 5 Weeks in Patients with CHD or CHD Risk Equivalents and an LDL-C \geq 130 mg/dL

	Simvastatin 20 mg	VYTORIN 10/10	VYTORIN 10/20	VYTORIN 10/40
N	253	251	109	97
Mean baseline LDL-C	174	165	167	171
Percent change LDL-C	-38	-47	-53	-59

In a multicenter, double-blind, 6-week study, 1902 patients with primary hyperlipidemia, 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).

Across the dosage range, when patients receiving VYTORIN were compared to those receiving milligram-equivalent statin doses of atorvastatin, VYTORIN lowered total-C, LDL-C, Apo B, and non-HDL-C significantly more than atorvastatin. Only the 10/40 mg and 10/80 mg VYTORIN doses increased HDL-C significantly more than the corresponding milligram-equivalent statin dose of atorvastatin. The effects of VYTORIN on TG were similar to the effects seen with atorvastatin. (See Table 9.)

Table 9
Response to VYTORIN and Atorvastatin in Patients with Primary Hyperlipidemia (Mean^a % Change from Untreated Baseline^b)

Treatment (Daily Dose)	N	Total-C ^c	LDL-C ^c	Apo B ^c	HDL-C	TG ^a	Non-HDL-C ^c
VYTORIN by dose							
10/10	230	-34 ^d	-47 ^d	-37 ^d	+8	-26	-43 ^d
10/20	233	-37 ^d	-51 ^d	-40 ^d	+7	-25	-46 ^d
10/40	236	-41 ^d	-57 ^d	-46 ^d	+9 ^d	-27	-52 ^d
10/80	224	-43 ^d	-59 ^d	-48 ^d	+8 ^d	-31	-54 ^d
Atorvastatin by dose							
10 mg	235	-27	-36	-31	+7	-21	-34
20 mg	230	-32	-44	-37	+5	-25	-41
40 mg	232	-36	-48	-40	+4	-24	-45
80 mg	230	-40	-53	-44	+1	-32	-50

^a For triglycerides, median % change from baseline

^b Baseline - on no lipid-lowering drug

^c VYTORIN doses pooled (10/10-10/80) provided significantly greater reductions in total-C, LDL-C, Apo B, and non-HDL-C compared to atorvastatin doses pooled (10-80).

^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 hyperlipidemia, 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 10).

Table 10
Response to VYTORIN and Atorvastatin in Patients with Primary Hyperlipidemia
(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≤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 hyperlipidemia, 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).

The effects of VYTORIN and rosuvastatin on total-C, LDL-C, Apo B, TG, non-HDL-C and HDL-C are shown in Table 11.

Table 11
Response to VYTORIN and Rosuvastatin in Patients with Primary Hyperlipidemia
(Mean^a % Change from Untreated Baseline^b)

Treatment (Daily Dose)	N	Total-C ^c	LDL-C ^c	Apo B ^c	HDL-C	TG ^a	Non-HDL-C ^c
VYTORIN by dose							
10/20	476	-37 ^d	-52 ^d	-42 ^d	+7	-23 ^d	-47 ^d
10/40	477	-39 ^e	-55 ^e	-44 ^e	+8	-27	-50 ^e
10/80	474	-44 ^f	-61 ^f	-50 ^f	+8	-30 ^f	-56 ^f
Rosuvastatin by dose							
10 mg	475	-32	-46	-37	+7	-20	-42
20 mg	478	-37	-52	-43	+8	-26	-48
40 mg	475	-41	-57	-47	+8	-28	-52

^a For triglycerides, median % change from baseline

^b Baseline - on no lipid-lowering drug

^c VYTORIN doses pooled (10/20-10/80) provided significantly greater reductions in total-C, LDL-C, Apo B, and non-HDL-C compared to rosuvastatin doses pooled (10-40 mg).

^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 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 were randomized to receive either simvastatin 40 mg or the coadministered active ingredients equivalent to VYTORIN 10/20. The median LDL-C and HbA1c levels at baseline were 89 mg/dL and 7.1%, respectively.

VYTORIN 10/20 was significantly more effective than doubling the dose of simvastatin to 40 mg. The median percent changes from baseline for VYTORIN vs. simvastatin were: LDL-C -25% and -5%; total-C -16% and -5%; Apo B -19% and -5%; and non-HDL-C -23% and -5%. Results for HDL-C and TG between the two treatment groups were not significantly different.

Ezetimibe

In two multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hyperlipidemia, 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, and baseline LDL-C.

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.

No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

14.2 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 3873 — Tablets VYTORIN 10/10 are white to off-white capsule-shaped tablets with code “311” on one side.

They are supplied as follows:

NDC 66582-311-31 bottles of 30

NDC 66582-311-54 bottles of 90

NDC 66582-311-82 bottles of 1000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-311-87 bottles of 10,000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-311-28 unit dose packages of 100.

No. 3874 — Tablets VYTORIN 10/20 are white to off-white capsule-shaped tablets with code “312” on one side.

They are supplied as follows:

NDC 66582-312-31 bottles of 30

NDC 66582-312-54 bottles of 90

NDC 66582-312-82 bottles of 1000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-312-87 bottles of 10,000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-312-28 unit dose packages of 100.

No. 3875 — Tablets VYTORIN 10/40 are white to off-white capsule-shaped tablets with code “313” on one side.

They are supplied as follows:

NDC 66582-313-31 bottles of 30

NDC 66582-313-54 bottles of 90

NDC 66582-313-74 bottles of 500 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-313-86 bottles of 5000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-313-52 unit dose packages of 50.

No. 3876 — Tablets VYTORIN 10/80 are white to off-white capsule-shaped tablets with code “315” on one side.

They are supplied as follows:

NDC 66582-315-31 bottles of 30

NDC 66582-315-54 bottles of 90

NDC 66582-315-74 bottles of 500 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-315-66 bottles of 2500 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-315-52 unit dose packages of 50.

Storage

Store at 20-25°C (68-77°F). [See USP Controlled Room Temperature.] Keep container tightly closed.

Storage of 10,000, 5000, and 2500 count bottles

Store bottle of 10,000 VYTORIN 10/10 and 10/20, 5000 VYTORIN 10/40, and 2500 VYTORIN 10/80 capsule-shaped tablets at 20-25°C (68-77°F). [See USP Controlled Room Temperature.] Store in original container until time of use. When product container is subdivided, repackage into a tightly-closed, light-resistant container. Entire contents must be repackaged immediately upon opening.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.5).]

Patients should be advised to adhere to their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program, and periodic testing of a fasting lipid panel.

Patients should be advised about substances they should not take concomitantly with VYTORIN [see Contraindications (4) and Warnings and Precautions (5.1)]. Patients should also be advised to inform other healthcare professionals prescribing a new medication or increasing the dose of an existing medication that they are taking VYTORIN.

17.1 Muscle Pain

All patients starting therapy with VYTORIN should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness. **Patients using the 10/80-mg dose should be informed that the risk of myopathy, including rhabdomyolysis, is increased with the use of the 10/80-mg dose.** The risk of myopathy, including rhabdomyolysis, occurring with use of VYTORIN is increased when taking certain types of medication or consuming larger quantities of grapefruit juice. Patients should discuss all medication, both prescription and over the counter, with their healthcare professional.

17.2 Liver Enzymes

It is recommended that liver function tests be performed before the initiation of VYTORIN, and thereafter when clinically indicated.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using VYTORIN. Discuss future pregnancy plans with your patients, and discuss when to stop taking VYTORIN if they are trying to conceive. Patients should be advised that if they become pregnant they should stop taking VYTORIN and call their healthcare professional.

17.4 Breast-feeding

Women who are breast-feeding should be advised to not use VYTORIN. Patients who have a lipid disorder and are breast-feeding should be advised to discuss the options with their healthcare professional.

17.5 FDA-Approved Patient Labeling

Issued June 2011

9619518



MERCK / Schering-Plough Pharmaceuticals

Manufactured for:
MERCK/Schering-Plough Pharmaceuticals
North Wales, PA 19454, USA

By:
MSD Technology Singapore Pte. Ltd.
Singapore 637766

Or

Merck Sharp & Dohme (Italia) S.p.A.
Via Emilia, 21
27100 – Pavia, Italy

Or

Merck Sharp & Dohme Ltd.
Cramlington, Northumberland, UK NE23 3JU

Or

Jointly manufactured by:
Merck Sharp & Dohme (Italia) S.p.A.

VYTORIN® (ezetimibe/simvastatin) Tablets

9619518

Via Emilia, 21
27100 – Pavia, Italy
and
MSD Technology Singapore Pte. Ltd.
Singapore 637766

U.S. Patent Nos. 5,846,966 and RE37,721

VYTORIN® (ezetimibe/simvastatin) Tablets

Patient Information about VYTORIN (VI-tor-in)

Generic name: ezetimibe/simvastatin tablets

Read this information carefully before you start taking VYTORIN. Review this information each time you refill your prescription for VYTORIN as there may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about VYTORIN, ask your doctor. Only your doctor can determine if VYTORIN is right for you.

What is VYTORIN?

VYTORIN contains two cholesterol-lowering medications, ezetimibe and simvastatin. VYTORIN is a prescription medicine used to lower levels of total cholesterol, LDL (bad) cholesterol, and fatty substances called triglycerides in the blood. In addition, VYTORIN raises levels of HDL (good) cholesterol. VYTORIN is for patients who cannot control their cholesterol levels by diet and exercise alone. You should stay on a cholesterol-lowering diet while taking this medicine.

VYTORIN works to reduce your cholesterol in two ways. It reduces the cholesterol absorbed in your digestive tract, as well as the cholesterol your body makes by itself. VYTORIN does not help you lose weight.

VYTORIN has not been shown to reduce heart attacks or strokes more than simvastatin alone.

The usual dose of VYTORIN is 10/10 mg to 10/40 mg 1 time each day.

VYTORIN 10/80 mg increases your chance of developing muscle damage. The 10/80 mg dose should only be used by people who:

- have been taking VYTORIN 10/80 mg chronically (such as 12 months or more) without having muscle damage
- do not need to take certain other medicines with VYTORIN that would increase your chance of getting muscle damage.

If you are unable to reach your LDL-cholesterol goal using VYTORIN 10/40 mg, your doctor should switch you to another cholesterol-lowering medicine.

For more information about cholesterol, see the section called “What should I know about high cholesterol?”

Who should not take VYTORIN?

Do not take VYTORIN if you take:

- Certain anti-fungal medicines including:
 - itraconazole
 - ketoconazole
 - posaconazole
- HIV protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir, tipranavir, or atazanavir),
- Certain antibiotics, including:
 - erythromycin
 - clarithromycin
 - telithromycin
- nefazodone
- A fibric acid medicine for lowering cholesterol called gemfibrozil
- cyclosporine

- danazol

Ask your doctor if you are not sure if your medicine is listed above.

Also do not take VYTORIN:

- If you are allergic to ezetimibe or simvastatin, the active ingredients in VYTORIN, or to the inactive ingredients. For a list of inactive ingredients, see the “Inactive ingredients” section at the end of this information sheet.
- If you have active liver disease or repeated blood tests indicating possible liver problems.
- If you are pregnant, or think you may be pregnant, or planning to become pregnant or breast-feeding.
- If you are a woman of childbearing age, you should use an effective method of birth control to prevent pregnancy while using VYTORIN.

VYTORIN has not been studied in children under 10 years of age.

What should I tell my doctor before and while taking VYTORIN?

Tell your doctor right away if you have unexplained muscle pain, tenderness, or weakness while you take VYTORIN. Muscle problems, including muscle breakdown, can be serious in some people and rarely cause kidney damage that can lead to death.

The risk of muscle breakdown is greater at higher doses of VYTORIN, particularly the 10/80 mg dose.

The risk of muscle breakdown is greater in people 65 years of age and older, females, and people with kidney or thyroid problems.

Taking VYTORIN with certain substances can increase the risk of muscle problems. It is especially important to tell your doctor if you take:

- fibric acid derivatives (such as fenofibrate)
- amiodarone (a drug used to treat an irregular heartbeat)
- verapamil, diltiazem, amlodipine, or ranolazine (drugs used to treat high blood pressure, chest pain associated with heart disease, or other heart conditions)
- large quantities of grapefruit juice (more than 1 quart daily)
- colchicine (a medicine used to treat gout)
- voriconazole (an anti-fungal medicine)
- large doses of niacin or nicotinic acid

Tell your doctor if you are taking niacin or a niacin-containing product, as this may increase your risk of muscle problems, especially if you are Chinese.

It is also important to tell your doctor if you are taking coumarin anticoagulants (drugs that prevent blood clots, such as warfarin).

Tell your doctor about all the medicines you take, including any prescription and nonprescription medicines, vitamins, and herbal supplements.

If you have more than 1 doctor, tell all of your doctors that you take VYTORIN. This is especially important when they prescribe a new medicine or increase the dose of your other medicines.

Tell your doctor about all your medical conditions including allergies.

Tell your doctor if you:

- drink substantial quantities of alcohol or ever had liver problems. VYTORIN may not be right for you.
- are pregnant or plan to become pregnant. Do not use VYTORIN if you are pregnant, trying to become pregnant or suspect that you are pregnant. If you become pregnant while taking VYTORIN, stop taking it and contact your doctor immediately.
- are breast-feeding. Do not use VYTORIN if you are breast-feeding.

Tell other doctors prescribing a new medication that you are taking VYTORIN.

How should I take VYTORIN?

- Take VYTORIN exactly as your doctor tells you to take it.
- Take VYTORIN once a day, in the evening, with or without food.
- If you miss a dose, do not take an extra dose. Just resume your usual schedule.
- Continue to follow a cholesterol-lowering diet while taking VYTORIN. Ask your doctor if you need diet information.
- Keep taking VYTORIN unless your doctor tells you to stop. If you stop taking VYTORIN, your cholesterol may rise again.

What should I do in case of an overdose?

Contact your doctor immediately.

What are the possible side effects of VYTORIN?

See your doctor regularly to check your cholesterol level and to check for side effects. Your doctor may do blood tests to check your liver before you start taking VYTORIN and during treatment.

In clinical studies patients reported the following common side effects while taking VYTORIN: headache, muscle pain, and diarrhea (see What should I tell my doctor before and while taking VYTORIN?).

The following side effects have been reported in general use with VYTORIN or with ezetimibe or simvastatin tablets (tablets that contain the active ingredients of VYTORIN):

- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing (which may require treatment right away), rash, hives; raised red rash, sometimes with target-shaped lesions; joint pain; muscle pain; alterations in some laboratory blood tests; liver problems (sometimes serious); inflammation of the pancreas; nausea; dizziness; tingling sensation; depression; gallstones; inflammation of the gallbladder; trouble sleeping; poor memory; erectile dysfunction; breathing problems including persistent cough and/or shortness of breath or fever.

Tell your doctor if you are having these or any other medical problems while on VYTORIN. This is not a complete list of side effects. For a complete list, ask your doctor or pharmacist.

What should I know about high cholesterol?

Cholesterol is a type of fat found in your blood. Cholesterol comes from two sources. It is produced by your body and it comes from the food you eat. Your total cholesterol is made up of both LDL and HDL cholesterol.

LDL cholesterol is called “bad” cholesterol because it can build up in the wall of your arteries and form plaque. Over time, plaque build-up can cause a narrowing of the arteries. This narrowing can slow or block blood flow to your heart, brain, and other organs. High LDL cholesterol is a major cause of heart disease and one of the causes for stroke.

HDL cholesterol is called “good” cholesterol because it keeps the bad cholesterol from building up in the arteries.

Triglycerides also are fats found in your body.

General Information about VYTORIN

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use VYTORIN for a condition for which it was not prescribed. Do not give VYTORIN to other people, even if they have the same condition you have. It may harm them.

This summarizes the most important information about VYTORIN. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about VYTORIN that is written for health professionals. For additional information, visit the following web site: vytorin.com.

Inactive ingredients:

Butylated hydroxyanisole NF, citric acid monohydrate USP, croscarmellose sodium NF, hypromellose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, and propyl gallate NF.

9619518



MERCK / Schering-Plough Pharmaceuticals

Manufactured for:
Merck/Schering-Plough Pharmaceuticals
North Wales, PA 19454, USA

This patient information has been approved by the U.S. Food and Drug Administration
Issued June 2011