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INTRODUCTION AND GUIDE TO THE READER

INTRODUCTION

A growing burden is being placed on our society by what has been termed a virtual epidemic of atherosclerotic cardiovascular disease (ASCVD), half of which is coronary heart disease (CHD). The American Heart Association estimates that approximately 62 million Americans have one or more types of cardiovascular disease (CVD) — 1 in 5 men and women have some form of CVD. Cardiovascular disease represents 40.1% of all deaths, or 1 of every 2.5 deaths—and over half of these deaths resulted from CHD. Elevated cholesterol is one of the major risk factors for CHD. The direct and indirect costs of cardiovascular diseases and stroke in the U.S. in the year 2004 are estimated at $368.4 billion.

The increase in CHD-associated morbidity and mortality continues to be a major concern in spite of the fact that the majority of causes of ASCVD are known and modifiable. In response to this significant public health concern, multiple guidelines have been created to assist health care professionals (HCPs) in the management of CVD. These guidelines emphasize the importance of healthy life style behavior, such as healthy diet and weight control, regular exercise, and avoidance of first- and second-hand smoking. When these measures are not adequate, pharmacologic intervention is recommended. A statin (HMG-CoA reductase inhibitor) is often the drug of choice for the control of elevated cholesterol.

Merck & Co., Inc. pioneered statin development, obtaining FDA approval in August 1987 for prescription lovastatin (MEVACOR™), the first drug of the statin class. Seventeen years later, there are over 27 million patient-treatment years of experience with MEVACOR™ in doses ranging from 10 to 80 mg, with the majority of prescriptions being written for the 20-mg dose. The efficacy and safety of MEVACOR™ has been well-established through the extensive marketed use of the product, and two postapproval megatrials, AFCAPS/TexCAPS and EXCEL (with approximately 15,000 men and women total).

There is an imperative for broader and more effective CHD risk factor modification, especially to reduce the impact of risk associated with total and LDL-cholesterol. A growing body of evidence demonstrates that cholesterol-lowering interventions decrease these risks for primary and secondary prevention patients. A nonprescription (over-the-counter [OTC]) lovastatin treatment-eligible population has been defined which is consistent with current guidelines for CHD prevention. This is a generally healthy primary prevention intermediate risk population with LDL-cholesterol between 130 and 170 mg/dL, and 2 or more CHD risk factors.

Johnson & Johnson◦Merck Consumer Pharmaceuticals Co., first sought FDA approval of an OTC lovastatin 10 mg product in 1999, and the data supporting this application were reviewed by the combined Nonprescription Drugs and Endocrine and Metabolic Drugs Advisory Committees in July 2000. Since that Advisory meeting, significant efforts have been made to address FDA and Advisory Committee concerns and learn more about the use of a statin in an OTC environment. Guidance from FDA and outside experts in CHD prevention was integral to identification of the target population, label paradigm and design Label Comprehension studies, as well as a large Actual Use clinical trial (CUSTOM). The result of these efforts is a product label and self-management system of educational and support materials that will assist the consumer in initially making (and continuing to make) appropriate decisions on product use and an overall approach to CHD risk reduction. J&J◦Merck is now seeking regulatory approval to market the 20-mg dose of lovastatin with the proposed tradename MEVACOR™ DAILY (referred to as MEVACOR™ OTC throughout most of this document) .

GUIDE TO THE READER

This Background Information document provides a comprehensive summary of the therapeutic rationale and data collected in support of the New Drug Application (NDA) for MEVACOR™ OTC 20 mg. The majority of information in this summary is extracted directly from documents included in the original 1999 OTC NDA submission and the 2004 amendment to that NDA. However, the presentation of some material differs somewhat from the regulatory submissions.

Synopsis: The Synopsis provides an overview of the MEVACOR™ OTC "story", and is intended to orient the reader to the key elements of the more detailed presentation that follows. In addition, two highly interrelated topics of major importance to the MEVACOR™ switch application, "Target population for an OTC statin" and MEVACOR™ OTC label criteria" are included in the Synopsis for the Advisory Committee's consideration.

Rationale for Nonprescription Lovastatin: This section reviews much of the growing epidemiologic and clinical evidence supporting the conclusion that the target OTC-eligible population is at risk of developing CHD and could benefit from safe and effective lipid-lowering therapy. It addresses such topics as the CHD burden currently facing our nation, the NCEP ATP III guidelines, the "Cholesterol Treatment Gap", the OTC statin-eligible population, the safety and efficacy of statins in general, as well as providing some features of the ZOCOR HEART-PRO (simvastatin 10mg) product, which was approved in the United Kingdom for nonprescription status. Examples of ZOCOR HEART-PRO label and support materials are also provided in an Appendix.

Efficacy of Lovastatin: This section summarizes the lipid modifying efficacy of lovastatin and CHD outcomes benefits, focusing primarily on the AFCAPS/TexCAPS and EXCEL mega-trial results. The lipid lowering results of the CUSTOM Actual Use study are also summarized.

Pharmacokinetics and Drug Metabolism of Lovastatin: The human pharmacokinetic properties of lovastatin are discussed in this section, with focus on special populations and potential for food or drug interactions.

Safety of Lovastatin: The safety profile of lovastatin is examined from several perspectives: controlled long-term mega-trials in over 15,000 patients at doses up to 80 mg/day, adverse experience reports from prescription marketing, and experience from OTC studies. Special attention is focused on topics associated with the statin class, including liver, muscle, drug interactions, and inadvertent use during pregnancy.

Mevacor OTC Self-Management System: J&J◦Merck has developed a program which accompanies the product designed to direct consumer behavior in safe, responsible and appropriate decision-making in the use of an OTC statin and overall CHD risk reduction. This includes a look at the various "tools" comprising the overall MEVACOR™ OTC Self-Management System (SMS) and the in-market plans to implement and maintain such a support system. Actual samples of the key components of this system and labeling are provided in an Appendix.

Consumer Behavior: This section describes the evolution of the treatment paradigm and the OTC labeling approach based on findings from consumer research, Label Comprehension studies and Actual Use studies. Most of the focus is on the CUSTOM study which tested the product label and support materials mentioned above.

Summary of Overall Benefit of OTC Access to Lovastatin 20 mg: This section integrates all of the previous information on potential benefits of nonprescription lovastatin, estimation of cardiovascular risk and risk reduction in the OTC-eligible population and the potential risks of OTC availability.

Overall Summary/Conclusions: This section brings together the conclusions that can be drawn from the vast amount of safety, efficacy, and consumer behavior data presented in this document.

Glossary of Abbreviations: Immediately following the Summary/Conclusions section, a complete list of abbreviations and the accompanying terms is provided to assist the reader in understanding the many medical, professional and organizational acronyms that appear throughout the document .

Reference List: A list of references, denoted in the text by numbers within brackets [ ], follows the Glossary of Abbreviations. These citations refer only to those journal articles and publications that are publicly accessible.

Appendices: A selection of relevant publication reprints and samples of MEVACOR™ OTC and ZOCOR™ HEART-PRO support materials are provided.

A. SYNOPSIS

1. Background

MEVACOR™ (lovastatin) has been available in the United States by prescription at doses of 10 mg to 80 mg since 1987. In 1996 Johnson & Johnson◦ Merck Consumer Pharmaceuticals Co. (J&J◦Merck) began work on an over-the-counter (OTC) lovastatin development program. A New Drug Application (NDA) was submitted by J&J◦Merck in late 1999 for a 10 mg dose of lovastatin. This initial MEVACOR™ OTC NDA submission was reviewed on July 13, 2000 by a joint session of the Endocrine & Metabolism and the Non-Prescription Drugs Advisory Committees. In brief, the Committees voted favorably on safety and lipid lowering efficacy but concluded that the outcome benefit of the 10 mg dose had not been adequately demonstrated and that additional consumer research was required. Since that time, J&J◦Merck and FDA have had multiple communications aimed at reaching consensus on establishing benefit, target OTC population, the OTC labeling paradigm, label testing methods and the design of a final Actual Use Study (CUSTOM). Additionally, FDA identified remaining safety concerns which would also need to be addressed within the J&J◦Merck research program. Following completion of this research, the MEVACOR™ OTC NDA was resubmitted in 2004 for the 20 mg dose and is now being presented again to the Endocrine & Metabolism and the Non-Prescription Drugs Advisory Committees.

2. Rationale and Potential Benefit of Nonprescription Lovastatin

2.1 Introduction

Public health in the United States has long been burdened by atherosclerotic cardiovascular disease, half of which is coronary heart disease (CHD) [1; 2; 3]. Elevated cholesterol is one of the most well documented risk factors for coronary heart disease (CHD). The relationship between both total cholesterol and LDL-cholesterol levels and CHD risk is strong and continuous with no evidence of a threshold within the ranges studied. CHD outcome studies for both primary and secondary prevention demonstrate that lowering LDL-cholesterol directly lowers risk for CHD events. Despite therapeutic advances which have reduced the mortality rate of a CHD event, the disease remains prevalent and is a leading cause of morbidity and mortality. Preventing the first CHD event also prevents the cascade of subsequent events which represent a substantial economic toll on our society.

Through the National Cholesterol Education Program (NCEP), NIH has addressed this public health crisis by creating clinical guidelines (the Adult Treatment Panel III Guidelines or ATP III, See Appendix D) for the management of elevated cholesterol and the associated CHD risk. Primary prevention with pharmacologic therapy is recommended along with therapeutic lifestyle changes (TLC) for intermediate risk individuals having two or more CHD risk factors and a 10-year risk of less than 20%.

Although much of the focus has been on higher risk populations and secondary prevention, significant opportunity to reduce the national burden of CHD lies in the prevention of the first event among those who are at moderate risk but not yet afflicted. Despite universal endorsement of the ATP guidelines by all major medical organizations, a profound cholesterol treatment gap continues to exist. Tens of millions of Americans for whom pharmacologic treatment and TLC is indicated remain untreated.

Statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors]) have been demonstrated to significantly modify the development and progression of atherosclerotic cardiovascular disease for both primary and secondary prevention populations at a wide range of CHD risk [4]. As noted in the 2002 American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute (ACC/AHA/NHLBI) Clinical Advisory on Statins (see Appendix E), certain of these drugs have been proven effective in reducing the incidence of CHD and total mortality, major coronary events (including MI), coronary revascularization procedures, stroke, and peripheral vascular disease [5]. The benefits of appropriate treatment with these drugs are believed to far outweigh their risks.

The reduction in risk associated with statin therapy has been demonstrated in long-term clinical trials for both primary prevention (AFCAPS/TexCAPS, WOSCOPS, and ASCOT) [6; 7; 8], and secondary prevention (4S, CARE, LIPID, and HPS) [9; 10; 11; 8]. Primary prevention studies evaluated the protective effects of statins in a "healthier" population at risk for a CHD event, whereas secondary prevention trials evaluated treatment of patients who already had a CHD event. CHD event rates are related to the LDL-C level achieved on treatment during the trial and there is log-linear relationship between LDL-C levels and CHD risk, even at low LDL-C concentrations. The Heart Protection Study (HPS) of simvastatin showed that reducing LDL-C lowers CHD risk regardless of the baseline cholesterol level. Statins thus hold great promise in the prevention and treatment of CHD. At present however, as the ACC/AHA/NHLBS Clinical Advisory points out, *"this potential has not been fully realized, because many patients at heightened risk are not being treated with these drugs. There is a well documented under-use of statins in clinical practice" [5]*.

The benefit of statin treatment in a primary prevention population with "average" cholesterol and moderate CHD risk was proven with lovastatin in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS, see Appendix A). This study targeted generally healthy middle-aged and older men and women without CHD who had characteristics reasonably similar to the proposed OTC target population [7]. After an average follow-up of 5.2 years, lovastatin 20 to 40 mg daily reduced the incidence of first acute CHD events (defined as fatal or nonfatal myocardial infarction [MI], unstable angina or sudden death) by 37% (p=0.00008); MI by 40% (p=0.002);

unstable angina by 32% (p=0.023); and coronary revascularization procedures by 33% (p=0.001) [7]. Based upon these data, MEVACOR™[1] (lovastatin) was approved by the FDA in 1999 at all doses for the primary prevention of MI, unstable angina, and coronary revascularization. More recently, AFCAPS/TexCAPS together with HPS formed the basis of the public health rationale for the July 2004 regulatory approval of nonprescription simvastatin 10 mg (ZOCOR ™[2] Heart-Pro) in the United Kingdom.

2.2 OTC Statin Target Population

The population proposed for OTC eligibility was targeted to be consistent with the current NCEP ATP III guidelines and was defined in collaboration with FDA and academic experts. Simply put, it is a *primary prevention intermediate risk* population with approximately a 10% to 20% risk of CHD over 10 years. The OTC labeling approach used to reach this risk group requires the user to have LDL-C between 130 and 170 mg/dL and two or more CHD risk factors, including age (men ≥45 years, women ≥55 years). The majority of individuals in this group must be able to achieve ATP III target treatment goals (LDL-C<130 mg/dL) using a low-dose statin without the need for titration. Therefore, the upper end of the LDL-C range is capped at 170 mg/dL because individuals with higher levels are unlikely to achieve the LDL-C treatment goal with the 20 mg dose of lovastatin, which provides about a 24% reduction in LDL-C in controlled clinical trials (see below).

Additionally, the OTC statin-eligible population should not have underlying chronic conditions that complicate self-management. Thus, individuals with active liver disease, LDL-C >170 mg/dL, diabetes, CHD, or history of stroke or other cardiovascular disease are not candidates for OTC statins and are directed by the OTC label to consult a physician. A more complete description of the MEVACOR™ OTC carton label is provided in Section 4 of this Synopsis and samples of actual label and consumer education and support materials are provide in Appendix I.

Using data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994) and Year 2000 U.S. population information, Ford et al estimate that the Year 2000 U.S. population includes 23 million individuals without CHD or a CHD equivalent who have 10-year risk for developing CHD in the 10% to 20% range [12]. Allowing for population growth since the Year 2000, this number may be significantly larger. Although the majority of these individuals are eligible for treatment according to ATP III, most are not being treated and current approaches to closing this cholesterol treatment gap have had only limited success. The National Academy of Science's Institute of Medicine (IOM) has thoroughly evaluated this type of systematic lack in medical attention in a range of therapeutic areas and termed this "The Quality Chasm". The conclusion of the IOM is that dramatic and innovative changes are required of the health care system.

[1] MEVACOR is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.
[2] ZOCOR is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

One of the underlying themes for change suggested by the IOM is the recognition of increased consumer participation in their own healthcare. This is consistent with the ever-increasing consumer movement toward a more proactive role in managing their own heart health. This public interest in maintaining or improving cardiovascular health is reflected in the wide array of food and dietary supplements that promote heart-healthy claims and the widespread use of low-dose aspirin for cardioprotection.

The proposed labeling and accompanying self-management system for MEVACOR™ OTC were designed to be part of a global approach to increase consumer action to reduce the risk of heart disease. Integral to this approach is not only OTC drug therapy for those at intermediate risk, but also directing higher CHD risk consumers to physician care and prescription therapy, and incorporation of lifestyle changes which embrace heart-healthy behaviors. This is accomplished by guiding consumers to determine their own eligibility to use the product and to achieve the target treatment goal required for continued use. Additionally, the importance of diet, exercise and healthcare professional involvement are key features of the labeling and self-management system.

2.3 CHD Benefit of Lovastatin 20 mg in an OTC Population

2.3.1 Effect on Lipids

The efficacy of lovastatin has been evaluated in two large-scale, long-term, randomized, placebo-controlled clinical trials. These studies, known as the Expanded Clinical Evaluation of Lovastatin (EXCEL) study and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), collectively analyzed for efficacy close to 15,000 participants. EXCEL (n=8,245) evaluated efficacy with respect to affecting the lipid profile with varying doses of lovastatin (up to 80 mg/day) for 48 weeks. AFCAPS/TexCAPS (n=6,605) evaluated the effects of lovastatin (at 20 and 40 mg/day) on both lipid profile and primary CHD events for 5.2 years. EXCEL evaluated high risk (mostly secondary prevention) participants whereas AFCAPS/TexCAPS studied predominantly (75%) intermediate risk primary prevention individuals. Both studies confirmed that after 12 to 18 weeks of therapy, users of lovastatin 20 mg/day are likely to achieve reductions of 17%, 24%, and 6% in Total-C, LDL-C, and triglycerides, respectively and a 7% increase in HDL-C.

2.3.2 Effect on CHD Risk Reduction

Because the AFCAPS/TexCAPS study population was generally similar to the proposed OTC treatment-eligible population, it is important to further examine the effect of lovastatin 20 mg on appropriate OTC-like subpopulations from AFCAPS/TexCAPS. In a post-hoc analysis conducted specifically to address this question, three subsets from AFCAPS/TexCAPS cohort were analyzed: 1) those that were eligible for MEVACOR™ OTC as per the proposed OTC label, 2) those who were OTC-eligible and remained on lovastatin 20 mg (non-titrators) throughout the study, and 3) those who were OTC-eligible and achieved the LDL-C target goal of <130 mg/dL. These three subpopulations

treated with lovastatin were compared with appropriately matched participants on placebo. Compared to placebo, there were highly significant reductions in the primary endpoint (defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) for all three subpopulations with point estimates ranging from 45% to 53% reduction. These reductions calculated by post-hoc analysis are consistent with the 37% reduction of the primary endpoint for the entire AFCAPS/TexCAPS cohort receiving lovastatin 20 and 40 mg/day.

The number needed to treat (NNT) to avoid a CHD event over the chosen 72-month (6 year) time period for Kaplan-Meier event rates is similar for these subpopulations (ranging from 25-28) and compares favorably with the overall NNT (34) from the lovastatin-treated population in AFCAPS/TexCAPS. Collectively, these analyses support the efficacy of lovastatin 20 mg in the primary prevention of CHD events in the proposed MEVACOR™ OTC label-eligible population.

3. Safety of Lovastatin in Marketed Use and in Large Long-Term Clinical Trials

The benefits of nonprescription lovastatin 20 mg must be weighed against potential risks. The safety of lovastatin in doses up to 80 mg has been well-established in nearly 25 years of investigative and marketed prescription use (estimated 27 million patient-treatment years since first marketed in 1987) and in two placebo-controlled mega-trials totaling nearly 15,000 men and women treated chronically (AFCAPS/TexCAPS had an average of 5 years of follow-up, and EXCEL was a 12-month trial) [7; 13]. In these controlled trials, the safety profile of the 20-mg daily dose was comparable to that of placebo. Also, a detailed review of all available post-marketing adverse experience reports revealed no previously unsuspected toxicity, a wide margin of safety in overdosage, and no suggestion of abuse potential. Three topics of special interest received a focused review in this document: drug class-related issues seen with all statins with regard to liver, muscle (including potential drug interactions), and use in pregnancy.

3.1 Liver

The primary site of action of statins is the liver and these agents are associated with occasional increased hepatic transaminase levels. This tendency is also seen with the other classes of cholesterol-lowering agents and is dose related. These elevations, characterized by minor elevations of ALT, are usually not associated with elevations of alkaline phosphatase or bilirubin. Larger elevations in transaminase levels are infrequent. In the 8,245-patient, 12-month EXCEL study, the incidence of two consecutive ALT elevations >3 x upper limit of normal (ULN) was 0.1% for both the lovastatin 20-mg and placebo groups, 0.9% for the 40-mg groups and 1.5% for 80 mg group. Transaminase levels decreased after discontinuing study drug. In AFCAPS/TexCAPS, consecutive AST/ALT elevations >3 x ULN occurred at similar frequency in those receiving placebo and lovastatin 20 to 40 mg, with most elevations resolving while continuing medication.

Now with years of experience with several statin drugs, the original concerns that occasional minor increases in liver transaminases might be indicative of a potential to cause more serious liver damage have proven to be unfounded. There is little evidence that these minor LFT elevations are predictive of hepatotoxicity. The ALT elevations are likely due to either increased ALT synthesis, decreased ALT clearance, or to enzyme leakage, possibly related to destabilization of cellular membranes due to a change in lipid content. These occasional asymptomatic elevations do not appear to be indicative of significant liver injury with lovastatin 20 to 40 mg/day.

Serious liver disease associated with lovastatin and statins in general appears to be very rare. The causal relationship between lovastatin and hepatitis or liver disease beyond asymptomatic increases in hepatic transaminases has not been established despite 27 million patient-treatment years of prescription use. Spontaneous reports of liver failure or hepatitis in patients treated with lovastatin reflect a wide range of different hepatobiliary pathologies and are not suggestive of a lovastatin-related pathogenesis. Individual reports are frequently confounded with concomitant medication and coexisting diseases. Finally, even if consumers with asymptomatic, undiagnosed liver disease use the OTC product, there is no evidence that the consumer is at any increased risk for worsening liver function [14; 15]. Thus, there should be no clinical concern that OTC users of the 20 mg dose will not be required to have blood tests for liver function. In fact, minor LFT elevations occur so frequently in the general population that LFT monitoring would result in numerous false positive signals.

Despite the demonstrated minimal hepatotoxic potential of lovastatin 20 mg, the proposed OTC label takes a cautious approach. The carton back panel label and package insert contraindicate use in consumers with active liver disease. This labeling has been shown effective in guiding consumers with known liver disease to not use the OTC product (see Section G. Consumer Behavior of this Background document).

3.2 Muscle

Myopathy is an adverse experience of interest associated with all statins. However, clinical study and marketed use experience indicate such occurrences are rare and dose related. Data from both EXCEL and AFCAPS/TexCAPS do not demonstrate a difference in the incidence of either myopathy or asymptomatic CK elevations >10 x ULN when placebo and lovastatin 20 mg and 40 mg treatment groups are compared. Progression to the more serious form, rhabdomyolysis is even rarer. A review published by FDA experts in 2002 reported that there have been approximately 0.19 cases of fatal rhabdomyolysis with lovastatin per one million prescriptions [16]. In 2004 another FDA publication confirmed the rarity of both fatal and non-fatal reports of this adverse event for all statins, except cerivastatin which was withdrawn from the market in 2001. [17; 18].

Potential for Drug Interactions: Co-administration of certain drugs with lovastatin could also affect the risk of myopathy. Fibrates (especially gemfibrozil) or niacin are independently associated with myopathy, and can interact pharmacodynamically with all statin drugs, apparently due to an effect on lipids rather than on specific inhibition of HMG-CoA reductase. In addition, lovastatin and some of the other statin drugs are metabolized by cytochrome P-450 3A4 (CYP3A4). Competitive inhibition by concomitant use of a few drugs similarly metabolized (e.g., cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, nefazodone and HIV protease inhibitors) can increase the circulating statin activity and therefore the potential for myopathy. Clinical experience with marketed lovastatin at doses of 10 to 80 mg has shown that while the relative risk of myopathy may be increased by an interacting drug, the absolute risk is still extremely low, particularly with the lower doses.

The AFCAPS/TexCAPS study was conducted before this CYP3A4 interaction was well understood and coadministration of the known inhibitors was not contraindicated. In this study over 500 lovastatin patients received strong CYP3A4 inhibitor(s) over the course of the over five year study. It is noteworthy and reassuring that there was no difference in the muscle side effect profile of either lovastatin 20 mg or 40 mg compared to a placebo group of equal size that also received the same CYP3A4 inhibitors (See Section E. Safety of Lovastatin of this Background document).

The symptoms of myopathy, sudden onset of unexplained muscle pain, muscle weakness or tenderness, can be recognized by patients and usually resolve with drug discontinuation. In order to protect against the rare serious clinical consequences, the OTC label and support materials warn in several places to discontinue treatment and consult a physician if such symptoms occur. As fibrates and strong CYP3A4 inhibitors are available by prescription only, physicians and pharmacists have an opportunity to reinforce avoidance of interacting medications. Furthermore, the label directs consumers to avoid medications that may interact with lovastatin and to inform their physician or pharmacist that they are taking OTC lovastatin when receiving new prescriptions. Therefore, due to the low incidence of myopathy, its symptomatic nature, and the information contained in the label, consumers will not be subject to undue risk when taking nonprescription lovastatin 20 mg.

3.3 Pregnancy

Use of lovastatin (and all statin drugs) during pregnancy has been contraindicated on the prescription label (Category X for use in pregnancy). This is required by regulation because of the lack of benefit of treating elevated lipids during that time frame and the non-specific findings in early rodent studies conducted at 40 to 80 times the human dose of lovastatin. Published animal studies [19] have since shown that the rodent fetal effects are caused indirectly by maternal toxicity associated with high doses rather than directly by fetal exposure to drug. Although a theoretical concern remains, no clear relationship between statin use and adverse pregnancy outcomes has been demonstrated in humans. Post-marketing reports of inadvertent human exposure during pregnancy do not indicate an association between lovastatin use and a pattern of adverse outcomes.

Nonetheless, because of the limited benefit of treatment during pregnancy and the lower level of CHD risk in premenopausal women, use of OTC lovastatin while pregnant or breast-feeding is strongly warned against in labeling materials. Furthermore, the OTC product is only indicated for women over age 55. However, should a woman be inadvertently exposed to lovastatin during the early stages of pregnancy, an adverse outcome related to the drug is highly unlikely.

3.4 Safety Conclusions

The extensive safety data (reviewed thoroughly in Section E) support the conclusion that lovastatin 20 mg can be safely marketed with appropriate labeling in the OTC environment for generally healthy individuals with moderately elevated cholesterol. The large margin of safety further mitigates concerns with potential consumer self-selection errors.

4. MEVACOR™ OTC Self-Management System

J&J◦Merck has developed a comprehensive global approach to direct consumer behavior to CHD prevention through a unique MEVACOR™ OTC "Self-Management System" (MOTC-SMS), designed to interactively empower consumers without leaving them unsupported. In addition to the outer carton Drug Facts label, the MOTC-SMS includes shelf display materials, package insert, a Quick Start Guide, educational brochure, video, product website, toll-free call center, and cholesterol testing referral service. A Consumer Assistance Program (called the Heart Health Program), which is a component of the MOTC-SMS, provides compliance and long term use support for consumers choosing to enroll. The Consumer Assistance Program consists of postcard reminders, e-mails, and periodic newsletters. Consumers can enroll through the toll free phone number, the website, or with the pharmacist at the point of purchase. These tools are provided to maximize effective communication and guide consumer behavior in using the product correctly when it is right for them, or in directing them to consult a physician for more comprehensive care (see Appendix I). The collaborative global approach is designed to encourage lifestyle changes and interaction with health care professionals (HCPs). Because low dose statin therapy in the OTC target population represents a "stepped care" approach to CHD risk management, an important indirect benefit will be to drive higher CHD risk individuals to their doctors for more individualized care.

J&J◦Merck has committed, as terms of NDA approval, to ensure that these same programs will be implemented in the marketplace along with appropriate HCP training. All printed materials are considered to be regulatory labeling and cannot be eliminated or changed without FDA approval.

As noted earlier, this overall label paradigm and target population (eligibility criteria) was developed with guidance from FDA and academic experts to be consistent with NCEP ATP III Guidelines. The MOTC-SMS focuses on the primary prevention of CHD in a subset of individuals with multiple (2 or more) risk factors and a 10-year CHD risk

of 10% to 20%. The cornerstone of the MEVACOR™ OTC Self-Management System is the carton label which is represented schematically on the next page. The language and format evolved from a series of iterative consumer research studies and was tested in a pivotal label comprehension study in which it scored well on all key measures, especially those directed at safety messages.

The proposed MEVACOR™ OTC carton label specifies that the product may be used, following a trial of diet and exercise, by individuals with LDL-C between 130 and 170 mg/dL, age (men ≥45 years, women ≥55 years), and one additional risk factor (smoking, family history, hypertension, or HDL <40 mg/dL). It is anticipated that the majority of consumers meeting these criteria will be able to reach their ATP III defined goal of LDL-C <130 mg/dL with daily use of the 20-mg dose of lovastatin. People with known current liver disease, history of muscle pain, weakness or tenderness while taking a cholesterol-lowering agent, pregnancy or breast-feeding, and allergies to lovastatin are directed by the label not to take the product. Consumers are directed by the label to seek physician or healthcare professional consultation for a number of situations.

Key Elements (not verbatim) of the Proposed MEVACOR™ OTC Carton Label

Use: To help lower LDL "bad" cholesterol, which may prevent a first heart attack.

Warnings

Do not use if:

- you have liver disease
- you have had any muscle pain, weakness, or tenderness from taking a cholesterol-lowering medicine
- you are pregnant or breast-feeding
- you know you are allergic to lovastatin or the inactive ingredients in this medicine

Ask your doctor or pharmacist before use if you are taking:

- any prescription medicine
- other cholesterol-lowering medicine (prescription or nonprescription)
- before starting new prescriptions: tell your doctor you are taking MEVACOR™ OTC

Do NOT use unless directed by your doctor if you have:

- very high LDL "bad" cholesterol above 170 mg/dL
- high triglycerides above 200 mg/dL
- healthy HDL "good" cholesterol above 60 mg/dL
- had a stroke
- ever had heart disease (heart attack or angina)
- diabetes

Stop use and ask your doctor if you develop any unexplained muscle pain, weakness or tenderness.

If you are diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.

How to decide if MEVACOR™ OTC is right for you

Before using you must have:

- Tried a healthy diet and exercise to reduce your cholesterol.
- Had a fasting cholesterol test within the last year.

Who can use: MEVACOR™ OTC is only for:

1. men 45 years or older **AND** women 55 years or older
2. people with LDL "bad" cholesterol between **130 to 170 mg/dL**
3. people with one or more of these conditions that increase heart disease risk:
   - You are a smoker
   - Low HDL "good" cholesterol under 40 mg/dL
   - Heart attack or angina in father or brother before 55; mother or sister before 65 **OR**
   - High blood pressure

Directions

1. **Take one tablet daily:**
   - Continue to eat a healthy diet and exercise.
2. **Test at 6 weeks: See if your LDL test result is below 129 mg/dL: "Yes" or "No"?**
   - NO – If at 6 weeks your LDL "bad" cholesterol is higher than 129 mg/dL, stop taking MEVACOR™ OTC. Talk to your doctor. MEVACOR™ OTC may not be enough for you.
   - YES – If at 6 weeks your LDL "bad" cholesterol is below 129 mg/dL, it's working, keep taking it daily and test your cholesterol once a year. If you stop, your cholesterol will go back up.
3. **Talk to your doctor if there is a change in your health:**
   - New prescriptions: Tell your doctor you are taking MEVACOR™ OTC before you begin taking any new prescription medicine.
   - New medical condition: If diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.
   - **Unexplained muscle pain: Stop use immediately** and talk to your doctor if you develop any unexplained muscle pain, weakness, or tenderness. This can be a sign of a rare but serious side effect.

4.1 Consumer Behavior Results From Actual Use Studies

The MOTC-SMS materials were evaluated in the lovastatin 20 mg Actual Use Study 084 titled: A **C**onsumer **U**se **S**tudy of **O**TC **M**EVACOR™ (CUSTOM). Since CUSTOM represents the current treatment paradigm, product labeling, and support materials, it provides the most relevant consumer behavior data. However, data are also available from three prior lovastatin 10 mg studies (Pharmacy Protocol 076, Restricted Access Protocol 079, and Red Arrow Protocol 081), and where relevant, these data will also be summarized. In CUSTOM, over 3,000 individuals evaluated MEVACOR™ OTC in a simulated pharmacy setting and over 1,000 elected to purchase and use the product for up to six months. The overall results of CUSTOM were recently published in the American Journal of Cardiology (AJC, see Appendix C) and analyzed further by Dr. Eric Brass of Harbor-UCLA Medical Center for Clinical Pharmacology in an AJC supplement (see Appendix F).

4.1.1 Cholesterol Knowledge and Accuracy of Self-Reported Values

Product advertising and labeling require the consumers to know their entire lipid profile before making a product purchase decision, or to consult with a physician before beginning to use nonprescription lovastatin. Data from CUSTOM and the lovastatin 10-mg studies were consistent in showing that consumers' knowledge of LDL-C and Total-C is sufficiently accurate to support appropriate purchase and use decisions. However, many consumers did not know their entire lipid profile including triglyceride levels, even though they were in a range of Total-C or LDL-C to benefit from using the product.

4.1.2 Self-Selection (Initial Use Decision)

Results from the CUSTOM Study demonstrated that:

- The majority (86%, 2,862/3,316) of consumers who evaluated nonprescription lovastatin appropriately chose whether or not to use the product
- Self-selection decisions among Users of nonprescription lovastatin that involved a potential for safety risk were rare (2%, 23/1,059)
- Inappropriate self-selection was often mitigated by interaction with a physician or by components of the MOTC-SMS (e.g., the toll-free number for eligibility verification).
- Many Users did not meet at least one of the multiple strict benefit criteria as defined by the carton label, yet still benefited from lipid lowering and were not exposed to safety risk

4.1.3 Self-Management of Treatment Over Time

The majority of consumers in CUSTOM appropriately self-managed their cholesterol over time, including treatment to goal, and changes in health status (new prescriptions, new medical conditions including unexplained muscle pain). A 21% to 25% reduction in LDL-C cholesterol was seen across all Users with 62% achieving their ATP III treatment goal of less than 130 mg/dL. The vast majority of Users (80%) had already tried diet and exercise and maintained or improved such heart-healthy habits while using the product. Substantial proportions of participants reported that they had consulted with their doctor either before or after they started taking MEVACOR™ OTC. This number was especially high (74%, 123/167) in those that were at higher CHD risk than specified by the label. This represents a significant indirect positive aspect of the MOTC-SMS. Lovastatin 20 mg was well-tolerated in this OTC setting, with one drug-related serious adverse event; a case of allergy to lovastatin which resolved without sequelae.

4.1.4 Long-Term Persistence and Compliance Results

Results from the CUSTOM and Pharmacy Studies demonstrated the following:

- Long-term persistence and compliance with lovastatin in a nonprescription setting compares favorably with published literature on experience with prescription statins.
- There is no evidence of excessive dosing on a chronic basis
- A substantial proportion of individuals who begin to use nonprescription lovastatin will persist with therapy over the long-term, will comply with daily dosing directions, and may thereby obtain substantial cholesterol reduction, with potential reduction in overall CHD risk.

4.1.5 Consumer Behavior Summary

The data from CUSTOM demonstrate that the MEVACOR™ OTC Self-Management System enables self-selection, appropriate de-selection, and self-management of elevated cholesterol by consumers in a manner consistent with the ATP III recommended LDL-C goal and guidelines. The CUSTOM study demonstrated that consumers at varying levels of risk for CHD benefit from the MEVACOR™ OTC Self-Management System. By and large, the targeted population of intermediate risk consumers is able to choose to use MEVACOR™ OTC and achieve LDL-C lowering and treatment-to-goal at rates similar to established medical care benchmarks, and readily partner with their physicians to achieve maximal benefit from drug therapy. As such, it represents an important option in an overall “stepped care” approach to CHD risk management. Moreover, the overall potential for safety concerns is minimal for consumers using the MEVACOR™ OTC Self-Management System.

The Actual Use studies have shown that there are a variety of ways to assist consumers in the decision process. Pharmacy personnel in locations with functioning community-based retail pharmacies can be trained to obtain the fingerstick lipid profiles and to guide the decision process appropriately should they be asked to do so by consumers in the marketplace. Non-medically trained product specialists can also effectively support the self-selection process through a toll-free telephone service.

5. Benefit Versus Risk Relationship of Nonprescription Lovastatin 20 mg

A global approach toward CHD risk reduction through the availability to consumers of over-the-counter lovastatin 20 mg will enable many individuals to self manage their cholesterol and maintain heart health. Access to the MEVACOR™ OTC Self-Management System will result in greater numbers of people interacting with their physicians to discuss cholesterol and coronary heart disease. Such access will also encourage the development of heart-healthy behaviors with maintenance and improvement in both exercise habits and dietary patterns. The availability of nonprescription lovastatin 20 mg will expand awareness of cholesterol management and cardiovascular risk factors among both the OTC-eligible and higher CHD risk population, encouraging more people at higher risk to seek comprehensive medical care. Quantitative estimates of the benefit in CHD events avoided in those self-medicating with lovastatin 20 mg over 6 years indicate that approximately 294 CHD events will be avoided or delayed per 10,000 people treated. The expansion of pharmacologic treatment to individuals with LDL-C between 130 mg/dL and 170 mg/dL by access to lovastatin 20 mg without a prescription will help to reduce the national burden of CHD.

Lovastatin 20 mg has proven to be extremely safe, and has a safety profile appropriate for use in the nonprescription setting. Patients participating in clinical trials have experienced few significant side effects, and post-marketing reports of adverse events have been very limited when considered in comparison to the very large number of people using lovastatin at prescription doses of 10 to 80 mg daily. Although myopathy occurs rarely, usually at higher doses, it is a symptomatic, reversible condition that can be managed by labeling. In rare instances, the consequences of potential drug interactions can be serious. Therefore, the label conveys simple warning messages reinforced multiple times and places. The risk of hepatotoxicity with lovastatin 20 mg is extremely low and routine measurement of transaminases is not necessary. A review of the reports of exposure during pregnancy uncovered no association between exposure to drug and a pattern of adverse pregnancy outcomes. However, nonprescription lovastatin will be indicated only for women $\geq$55 years of age and will be contraindicated in pregnancy and breast-feeding. Overall, the potential safety risks are exceedingly low and can be managed with appropriate warnings in the label, together with the overall MEVACOR™ OTC Self-Management System.

Effective product labeling and reinforcement tools integrated within the MEVACOR™ OTC Self-Management System (including the package circular, educational information, and toll-free call support line to product specialists) will guide consumers toward appropriate self-selection and continued use of nonprescription lovastatin 20 mg. Therapeutic lifestyle patterns (such as diet and exercise) will be emphasized and maintained with the MEVACOR™ OTC Self-Management System which also encourages healthcare professional interactions for both users and non-users of the product. The benefit-to-risk relationship for lovastatin 20 mg can be compared favorably to that observed with OTC low-dose aspirin therapy for the prevention of CHD. The overall direct and indirect benefits of nonprescription availability lovastatin 20 mg far outweigh any foreseeable risks resulting in a favorable benefit/risk ratio.

6. Points to Consider

There are a variety of topics upon which the FDA Advisory Committees may be asked to deliberate. The traditional questions for an OTC switch proposal generally focus on efficacy in the OTC indication and the safe use of the product if made available to consumers without the involvement of a physician. Other common issues include the potential of the consumer under-treating a condition which may be more serious or, conversely, over-treating a condition which is not appropriate or serious enough for drug therapy. These are also important topics for the MEVACOR™ switch proposal, and are examined in depth in this document. Additionally, there are two highly inter-related topics of major importance which are specific to the MEVACOR™ switch application and are summarized as follows.

Target Population for an OTC Statin: As noted previously, the population targeted for OTC statin eligibility has been established with guidance from FDA and academic experts with an overall intent to be consistent with the treatment recommendations defined by the NCEP ATP III guidelines. ATP III has defined the target primary prevention group with a 10% to 20% 10-year CHD risk as eligible for pharmacologic therapy, with an LDL-C treatment goal of <130 mg/dL. A given patient's CHD risk may be estimated by using the Framingham Risk Equation. The lower boundary of 10% was established by NCEP largely on a cost-effectiveness basis. However, as demonstrated by AFCAPS/TexCAPS, CHD prevention benefit can be achieved at 10-year risk levels below 10%. Furthermore, there is a growing body of evidence that, at 10-year risk levels below 15%, the Framingham model tends to underestimate risk in certain populations [20; 21].

The approach of having consumers calculate their own Framingham Risk score was carefully assessed by J&J◦Merck and found to be impractical in an OTC setting. In fact, this approach is usually not carried out according to ATP III in a clinical setting. Therefore, a label incorporating surrogates to allow self-selection of a population of appropriate risk level was designed and tested. The multi-factorial elements of the MEVACOR™ OTC labeling paradigm are aimed at approximating this population as

closely as possible through the surrogates of LDL-C criteria and CHD risk factor assessment. In so doing, consumers are asked to assess multiple criteria of varying degrees of importance. For instance, they are required to know their cholesterol in terms of LDL-C together with HDL-C and triglyceride levels. Different paradigms for defining a target population have also been explored. For example, the approach taken with the UK ZOCOR Heart-Pro label (See Section B.10 and Appendix J), is based entirely on risk factor assessment without requiring knowledge of lipid levels.

Given this multi-factorial approach proposed for MEVACOR™ OTC, it should come as no surprise that a substantial number of Users in CUSTOM did not meet all of the specific label eligibility criteria relating to benefit (although many consulted a physician, which technically meets label requirements). For this reason, some may interpret the outcome of the CUSTOM study as relatively negative if assessed rigorously in terms of pure label compliance. However, 100% adherence to each aspect of the selection criteria is not critical to appropriate self-selection in this indication of lipid lowering and CHD risk reduction. This more global approach to interpreting behavior is in contrast to traditional OTC product indications for symptomatic conditions or safety warnings, where each message/criterion is often independently important. Indeed, in CUSTOM there was a high level of adherence to the label safety criteria.

Similarly, many of the Users in CUSTOM would be estimated to be outside of the 10% to 20% 10-year risk ATP III target and ideally would not be prospectively targeted to use MEVACOR™ OTC. However, analysis of this population suggests a substantial health benefit would be achieved despite the somewhat lower or higher average absolute risk (see E. Brass analysis in Appendix F). Thus, the label meets its objectives. While not meeting a high "heeding standard" in the traditional sense, it represents an appropriate and validated OTC label through use of surrogates to reach the intended target population.

MEVACOR™ OTC Label Criteria: As explained above, the multi-factorial elements of the proposed labeling paradigm are driven by the importance of adhering as closely as possible to the recommendations of the ATP III guidelines, including treatment to goal. Nonetheless, the majority of Users in CUSTOM can derive CHD risk reduction from use of lovastatin 20 mg, despite their varying degrees of ineligibility according to each of the strict terms of the label. Very importantly, the Advisory Committees should be aware that J&J◦Merck believes that there is opportunity to improve and perhaps simplify the proposed label. The CUSTOM study has shown that a multi-factorial label can attract the appropriate, if not exactly correct, population that can safely use and benefit from the achievable lipid lowering. However, J&J◦Merck remains completely open to Committee and FDA recommendations for alternative wording or eligibility criteria which will serve to maximize the safe and effective use of the product by the right people.

7. Overall Summary

The OTC Statin-Eligible Population is at risk for the future development of coronary heart disease. The 20 mg dose of lovastatin has been demonstrated to provide substantial lowering of LDL cholesterol with proven CHD risk reduction over the long term in an OTC-like population. This population is eligible for therapy with statins based on current guidelines. Despite this, an enormous cholesterol treatment gap exists for treating and preventing coronary heart disease in the present health care system. The Institute of Medicine (IOM) has suggested a redesign for the shortcomings of our current health care system that also serves to address this cholesterol treatment gap. The availability of the MEVACOR™ OTC Self-Management System would be entirely consistent with the design and intent of the IOM's Quality Chasm Report. The MEVACOR™ OTC Self Management System is one of many solutions with great potential to enhance the public good by helping to reduce extraordinarily high levels of morbidity and mortality from atherosclerotic cardiovascular disease and the associated direct and indirect societal costs. Lovastatin is particularly well-suited as an adjunct to diet and exercise for primary prevention in the OTC population because of its many years of clinical experience and proven safety record.

The MEVACOR™ OTC Self Management System has been specifically designed to address the cardiovascular needs of the current and evolving health care system. It is consistent with a global approach to the cholesterol treatment gap, incorporating pharmacologic therapy with education, lifestyle changes and encouragement of a partnership with the health care professional. The availability of an OTC statin option will have a meaningful impact in improving the CHD risk status of intermediate risk Americans and thereby help to reduce the burden of CHD over the long term.

B. RATIONALE FOR NONPRESCRIPTION LOVASTATIN

1. Introduction

The public health of the United States is being undermined by a virtual epidemic of atherosclerotic cardiovascular disease (ASCVD), half of which is coronary heart disease (CHD) [1; 2; 3]. Despite therapeutic advances that have reduced the mortality rate of a CHD event in recent years, the disease remains prevalent and a leading cause of mortality and disability. Preventing the first CHD event prevents the cascade of subsequent events that represent a substantial economic burden to our society. The National Heart, Lung, and Blood Institute has addressed this public health crisis by issuing updated guidelines in 2001 (known as the Adult Treatment Panel III Guidelines or ATP III) [22]. These guidelines call for significant lifestyle changes in order to normalize blood levels of cholesterol – one of the major risk factors for ASCVD. If such lifestyle changes fail, pharmacologic therapy is recommended.

Despite universal endorsement of these guidelines by all major medical organizations, a profound cholesterol treatment gap exists (see Appendix B). The result of this cholesterol treatment gap is that tens of millions of Americans for whom treatment is indicated either remain untreated or are inadequately treated to target goal LDL cholesterol (LDL-C). Certain drugs (including statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors]) have been demonstrated to significantly modify the development and progression of ASCVD for both primary and secondary prevention.

Using data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994) and Year 2000 U.S. population information, Ford et al. estimate that the year 2000 U.S. population (age 20 to 79 years) includes 23 million individuals without CHD (or a CHD equivalent), but with a 10-year risk for developing CHD in the 10% to 20% range [12]. **The U.S. population also includes a large number of individuals with multiple risk factors whose 10-year CHD risk is <10%. This latter population has been termed "moderate risk," to distinguish them from the 10-20% risk group that are at "moderate high risk." Together, both groups comprise the intermediate risk population [23].**

The majority of these individuals are not currently being treated with statins, and current approaches to closing this gap have had limited success at best. The National Academy of Science's Institute of Medicine (IOM) has thoroughly evaluated this type of systematic lack in medical attention in a range of therapeutic areas, and has termed this "The Quality Chasm" [24]. The conclusion of the IOM is that dramatic and innovative changes are required of the health care system. Importantly, one of the underlying themes for change suggested by the IOM is the recognition of increased consumer participation in healthcare.

Consumers are currently spending billions of dollars on unproven preventatives and remedies for a range of conditions that include CHD. Such food and dietary supplements for CHD need to be addressed with safe and efficacious alternatives. One such alternative is the MEVACOR™[3] OTC Self-Management System which is uniquely suited to target the intermediate CHD risk population [23]. Such a unique system could be both beneficial and cost-effective. An OTC Self-Management System of the type proposed here can also increase overall heart health awareness and channel appropriate people to a physician for more aggressive treatment.

2. The CHD Burden in the United States

The American Heart Association (AHA) estimates that ~62 million Americans have one or more types of cardiovascular disease (CVD). One in 5 men and women have some form of CVD—the number one cause of death in the United States claiming close to 1 million lives in the Year 2000 [1; 3]. CVD represents 40.1% of all deaths or 1 of every 2.5 deaths. In 2000, there were 1.74 times as many deaths from CVD as from malignancy [1]. Over half of these deaths resulted from CHD. CHD-associated morbidity and mortality continues to be a major concern and has been especially neglected in women and minorities [1; 25; 3]. This increase in incidence and prevalence of CHD is occurring in spite of the fact that the majority of causes of atherosclerotic cardiovascular disease are known and modifiable [26]. Hypercholesterolemia is one of the major risk factors for CHD [27; 28]. Using data derived from NHANES III, the AHA 2004 Update estimates that at least 105 million Americans between the ages of 20 to 74 years have an elevated total cholesterol of 200 mg/dL or higher [3].

The direct and indirect costs of cardiovascular diseases and stroke in the United States in 2004 are estimated at $368.4 billion [3]. All forms of heart disease account for $238.6 billion; specific forms of heart disease account for spending $133.2 billion on CHD, $53.6 billion on Stroke, $55.5 billion on Hypertensive Disease, and $28.8 billion on Congestive Heart Failure.

In response to this public health concern, multiple guidelines have been created to assist health care professionals (HCPs) in the management of CVD. All of these guidelines emphasize the necessity of stratifying patients by level of risk and matching the intensity of intervention to the hazard for cardiovascular disease events [26]. Adoption of healthy life habits remains the cornerstone of primary prevention. Avoidance of smoking (including secondhand smoke), weight control, adapting a healthy dietary pattern, and engaging in a regular and appropriate exercise program are key to this healthy lifestyle.

[3] MEVACOR is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

When these healthy lifestyle changes are insufficient, pharmacologic intervention should be considered. As such, statins are often the drugs of choice for the pharmacologic control of elevated cholesterol in the treatment and prevention of CHD. The decision to use lipid-lowering drugs is determined by CHD risk stratification. As stated in the 2002 AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke [26]: HCPs need "to engage greater numbers of patients, at an earlier stage of their disease, in comprehensive cardiovascular risk reduction with the use of interventions that are designed to circumvent or alleviate barriers to participation and adherence, so that many more individuals may realize the benefits that primary prevention can provide. The HCP should create an environment supportive of risk factor change, including long-term reinforcement of adherence to lifestyle and drug interventions. The availability of an effective OTC Self-Management System utilizing an established statin (with proven safety, and long-term CHD outcomes) that complements the role of the HCP would contribute towards meeting these goals.

3. The NCEP ATP III Guidelines

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines [22; 29] are endorsed by the ACC, AHA, and NHLBI. The ATP III guidelines identify LDL cholesterol (LDL-C) as the primary target of therapy. ATP III establishes goals for LDL-C that are dependent upon an individual's 10-year CHD risk status, as assessed by the Framingham Risk Assessment Scoring Measure [22]. If LDL-C goals are not achieved by therapeutic lifestyle changes, pharmacologic therapy is recommended. The therapeutic agents of choice are statins. While ATP III maintains attention to intensive treatment of individuals with CHD, its major new feature (compared with earlier versions) is a focus on primary prevention in persons with multiple (2 or more) risk factors. **The MEVACOR™ OTC Self Management System is focused on the primary prevention of CHD in persons with multiple (2 or more) risk factors and a CHD risk of 10% to 20%. The MEVACOR™ OTC Self-Management System targets the population that is unlikely to be receiving therapy with statins.** In accordance with the ATP III guidelines, more than 37 million people are now considered to be eligible for lipid-lowering therapy with statins (recommended as the first-line drug of choice by ATP III) [30]. Because these data are based on the NHANES III survey, a U.S. population survey taken between 1988 to 1994, this figure may now be significantly greater. As part of the ACC/AHA/NHLBI Clinical Advisory on Statins (see Appendix E), "this broad expansion of statin use will require that increased attention be given to every aspect of statin therapy (i.e., efficacy, safety, and cost-effectiveness)."

In accordance with ATP III, HCPs are being asked to quantify the 10-year risk of all primary prevention individuals with 2 or more risk factors using the Framingham Risk Assessment Scoring Measure. This global risk assessment instrument assigns risk levels according to absolute risk of CHD (derived from totaling risk points assigned for the presence or absence, or degree of severity, of a number of risk factors, including the patient's sex, age, total cholesterol level, smoking status, high density lipoprotein cholesterol (HDL-C) level, and systolic blood pressure).

According to ATP III, pharmacologic therapy is indicated for all individuals with multiple risk factors (2 or more) whose 10-year risk is ≤20% if they have not achieved target LDL-C of <130 mg/dL by therapeutic lifestyle change (TLC). Lipid-lowering therapy should also be considered for low risk individuals if, after an adequate trial of dietary therapy, the LDL-C is ≥190 mg/dL. When serum LDL-C ranges from 160 to 189 mg/dL, introduction of a cholesterol-lowering drug is a therapeutic option for individuals in appropriate circumstances, such as when a severe risk factor is present. Such severe CHD risk factors include continued cigarette smoking, a strongly positive family history of premature atherosclerotic CVD, elevated triglycerides (≥200 mg/dL) plus elevated non-HDL-C (≥160 mg/dL), low HDL-C (<40 mg/dL), the metabolic syndrome, and/or the presence of emerging risk factors (e.g., serum high-sensitivity C-reactive protein, >3 mg/L or coronary calcium >75th percentile for a person's age and sex [31]. Recently, more aggressive treatment goals have been identified for high risk individuals [31], and are incorporated into Table B-1. The proposed MEVACOR OTC Self-Management System targets the moderate to moderately high risk group (10-year risk 10% to 20%) with an LDL-C goal of <130 mg/dL. OTC eligibility should also be considered for those individuals with 0 to 1 risk factors and a 10-year risk of <10% (designated by ATP III as low risk), with a target LDL-C goal of <160 mg/dL.

Table B-1

Updated ATP III LDL-C Criteria for Goals
and Initiating Therapeutic Lifestyle Changes or Drug Therapy

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy
High risk: CHD[*] or CHD risk equivalents[†] (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)[|]	≥100 mg/dl[#]	≥100 mg/dL[††] (<100 mg/dL: consider drug options)[‡‡]
Moderately high risk: 2 + risk factors[‡] (10-year risk 10% to 20%)[§§]	<130 mg/dL[¶]	≥130 mg/dL[#]	≥130 mg/dL (100-129 mg/dL; consider drug options)
Moderate risk: 2 + risk factors[‡] (10-year risk <10%)[§§]	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0-1 risk factor[§]	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

[*] CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

[†] CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2 + risk factors with 10-year risk for hard CHD >20%.

[‡] Risk factors include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥55 years).

[§] Almost all people with zero or 1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.

[|] Very high risk favors the optional LDL-C goal of <70 mg/dL, and in patients with high triglycerides, non-HDL-C <100 mg/dL.

[¶] Optional LDL-C goal <100 mg/dL.

[#] Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolis syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

[††] If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

[‡‡] For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.

Adapted from ATP III Updated Report July 13, 2004 [31]

4. The Cholesterol Treatment Gap

Based on ATP III guidelines, more than 37 million people in the United States now qualify for drug therapy in the treatment and management of hypercholesterolemia [22; 29]. Current data indicate that only 38% of primary prevention individuals are being treated for hypercholesterolemia[32]. Thus, almost 13 million Americans who qualify for primary prevention of CHD are untreated. The vast majority of individuals who have hypercholesterolemia are under-treated or not treated at all (commonly known as the "Cholesterol Treatment Gap"). Many of these individuals would clearly benefit from preventative strategies [27].

The Cholesterol Treatment Gap has been identified to include patients treated within cardiology subspecialty practices [33; 34], postmenopausal women (especially African Americans) [35; 36; 37], and the elderly [38]. Due to continued emphasis on the secondary prevention population, it is expected that the treatment gap will remain large among the primary prevention population.

Treatment to goal is not being achieved in patients who are taking statins for either primary or secondary prevention. Pearson et al. reported on the use of lipid-lowering agents in the Lipid Treatment Assessment Project (L-TAP) study involving 4888 patients from all regions of the United States in 1997 [39]. Of those patients with known CAD, only 18% were treated to target LDL-C goal of ≤100 mg/dL. Of those with 2 or more risk factors and no evidence of CHD, only 37% were treated to target LDL-C goal of <130 mg/dL. Lastly, of those with less than 2 risk factors, only 68% achieved their target LDL-C goal of <160 mg/dL.

There is a significant Cholesterol Treatment Gap among primary prevention patients who qualify for lipid lowering therapy based on the presence of multiple (2 or more) CHD risk factors. Dubois et al. [40] used an administrative database from 1999 of medical and pharmaceutical claims (that included managed care plan enrollees in 22 states) to assess lipid treatment rates in the group of patients who collectively had 2 or more risk factors (hypertension, tobacco use, obesity), age risk factor (men ≥45 years; women ≥55 years) plus 1 additional risk factor, or hypercholesterolemia/hyperlipidemia diagnosis only. He found only 18% to be on lipid lowering therapy. More recently (2001), Nag et al. identified the cholesterol treatment gap to be 62% among individuals with multiple risk factors and elevated LDL-C levels [32].

5. Efficacy of Statins in Treating Coronary Heart Disease

As noted in the American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute (ACC/AHA/NHLBI) Clinical Advisory on Statins (see Appendix E) these drugs are very effective in reducing the incidence of CHD and total mortality, major coronary events (including MI), coronary revascularization procedures,

stroke, and peripheral vascular disease. The benefits of certain statins have been demonstrated in both men and women, especially in middle-aged and older persons, for both primary and secondary prevention. Statins "reduce the risk of essentially every clinical manifestation of the atherosclerotic process; they are easy to administer, with good patient acceptance". Statins thus hold great promise in the treatment of CHD. At present however, as the ACC/AHA/NHLBI Clinical Advisory points out, "this potential has not been fully realized, because many patients at heightened risk are not being treated with these drugs. There is a well documented under-use of statins in clinical practice".

In cases where individual statins have been studied, a consistent and highly significant reduction in CHD risk has been achieved regardless of level of risk, patient age, or presenting lipid profile [4; 9; 6; 10; 41; 11; 7; 42; 8; 43; 44; 45; 46]. A 1 mmol/L (equivalent to ~40 mg/dL) reduction in plasma low density lipoprotein cholesterol (LDL-C) concentration maintained for about 5 years reduced the risks of coronary events, of strokes, and of revascularization procedures by about 25% [4]. As shown in Table B-3, this reduction in risk associated with statin therapy has been demonstrated in long-term clinical trials (lasting ~5 years) for both primary (AFCAPS/TexCAPS, WOSCOPS, and ASCOT) [6; 7; 8] and secondary prevention (4S, CARE, LIPID, and HPS) [9; 10; 11; 8]. Primary prevention studies evaluated the prophylactic nature of statins in a "healthier" population at risk for a CHD event whereas secondary prevention trials evaluated patients who already had a CHD event. As shown in Figure B-1, CHD event rates are related to the LDL-C level achieved on treatment during the trial. Secondary prevention trials (involving patients with known CHD) had higher event rates than primary prevention trials (involving patients without CHD).

Table B-3

Effect of Statin Therapy on Coronary Heart Disease:
Clinical Events Trials

Trial[†] (Duration)	Baseline LDL-C (mg/dL)	Reduction in LDL-C	LDL-C Achieved (mg/dL)	Statin Event[‡] Rate	Placebo Event[‡] Rate	RRR	ARR	NNT
Primary Prevention Trials								
AFCAPS/ TexCAPS (5.2 yr) [7] (n=6605)	150	25%	115	3.5%	5.5%	37%	2.0%	50
WOSCOPS (4.9 yr) [6] (n=6595)	192	26%	159	5.3%	7.5%	29%	2.2%	46
ASCOT (3.3 yr) [46] (n=19342)	133	29%	90	1.9%	3.0%	36%	1.1%	91
Secondary Prevention Trials								
4S (5 yr) [9] (n=4444)	188	35%	122	19.4%	28.0%	34%	8.5%	12
LIPID (6.1 yr) [11] (n=9014)	150	25%[§]	112	12.3%	15.7%	23%	3.4%	30
CARE (5 yr) [10] (n=4139)	139	32%	98	10.2%	13.2%	24%	3.0%	34
HPS (5 yr) [8] (n=20,536)	131	44	73	16.1%	20.8%	23%	4.7%	21

(Modified from [8; 47]).
(RRR = Relative risk reduction; ARR = Absolute risk reduction; NNT = Number needed to treat.)

[†] Pravastatin 40 mg/day was evaluated in CARE, LIPID, and WOSCOPS;
Simvastatin was evaluated at 20 to 40 mg/d in 4S and 40 mg/d in HPS.
Lovastatin 20 to 40 mg/day was evaluated in AFCAPS/TexCAPS.
Atorvastatin 10 mg/day was evaluated in ASCOT.

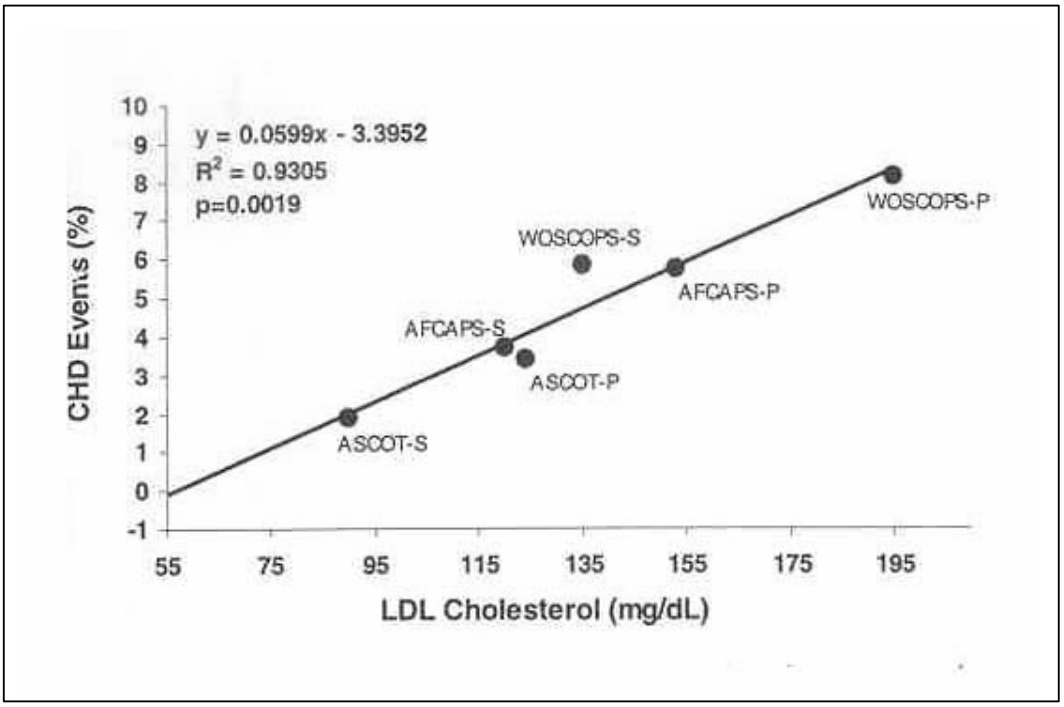
[‡] Primary Outcome:
WOSCOPS, CARE, LIPID: nonfatal MI or CHD death.
AFCAPS: nonfatal or fatal MI, unstable angina, or sudden cardiac death as first event.
4S: nonfatal MI, coronary death, or resuscitated cardiac arrest.
HPS: mortality and fatal or nonfatal vascular events in primary prevention subgroup.
ASCOT: nonfatal MI and fatal CHD. Rate per 1000 patient-years.

[§] Versus placebo.

A measurement of efficacy often used by clinicians and epidemiologists to assess the benefit of drug treatment is number needed to treat (NNT). The NNT is defined as the reciprocal of the absolute risk reduction for a particular treatment. The NNT is a useful measure of the clinical impact of a drug and indicates the number of people who must be treated with the drug over a period of time in order to prevent one event. The NNT allows for the determination of whether the treatment benefits seen with a drug exceed the potential risks [48]. The NNT is both treatment specific and disease population specific. NNTs for a specified intervention depend upon the baseline risk for a condition (i.e., the probability at baseline that the patient population being considered will experience the outcome of interest) being similar among populations studied. For the same relative risk reduction, the NNT will be greater in a population with a lower event rate (i.e., a healthier population). Each of the statin trials listed in Table B-3 evaluated different risk populations for either primary or secondary prevention. Despite this, the NNTs for the primary prevention trials (AFCAPS/TexCAPS, ASCOT and WOSCOPS) and those for the secondary prevention trials (4S, LIPID, CARE, and HPS) are very compelling and readily justify the utility of certain statins for treating at risk patients. The NNTs from these trials were calculated based on varied periods of time as appropriate for each individual study.

Figure B-1

Cardiac Event Rates by LDL-C Level Achieved in Statin Trials in Primary Prevention Populations



P = Placebo group S = Statin group

[49]

As demonstrated by the 5.3-year MRC/BHF Heart Protection Study (HPS) utilizing simvastatin 40 mg or placebo once daily in 20,536 high risk patients with established CVD or diabetes, those patients presenting with baseline LDL-C levels of <100 mg/dL (2.6 mmol/L) (n=3421) showed similar degrees of risk reduction (282 major vascular events [16.4%] versus 358 major vascular events [21.0%]; p=0.0006) as those patients presenting with much higher levels of LDL-C (≥130 mg/dL) [8]. These "findings indicate that any thresholds below which lowering LDL cholesterol does not safely reduce risk are at much lower concentrations (e.g., below 2 mmol/L) than are typically seen in Western populations" [4]. According to the 13-Jul-2004 NCEP updated ATP III Report: "HPS provides strong new evidence to support the log-linear relationship between LDL-C levels and CHD risk, even at low LDL-C levels. In fact, HPS results suggest that reducing serum LDL-C from any baseline level further lowers risk in

high-risk patients" [31]. The results of HPS together with AFCAPS formed the basis of the public health rationale for approval of nonprescription ZOCOR™[4] (simvastatin) in the United Kingdom (see B.10 of this Section).

Although most of the clinical benefit obtained from statins is a direct result of their lipid-lowering properties, these agents appear to display additional *cholesterol-independent effects* on various aspects of cardiovascular disease [50]. These so-called pleiotropic effects may involve improvement in endothelial function, decreasing vascular inflammation, and enhancing plaque stability.

6. Safety of Statins

See also Section E of this background document for a more comprehensive review of the safety of lovastatin.

6.1 Myopathy and Rhabdomyolysis

The safety of statins as a class has recently been reviewed by the ACC/AHA/NHLBI in a Clinical Advisory to health care providers (HCPs) [5]. The focus of this Advisory was on myopathy as it relates to statin use. The ACC/AHA/NHLBI Clinical Advisory concludes that "statins have proven to be extremely safe in the vast majority of patients receiving them. Few significant side effects were observed in clinical trials, and post-marketing reports of adverse events have been very limited when considered in comparison to the very large number of persons safely receiving these drugs." The Advisory notes that statins are "not entirely free of side effects" and, as is the case with all drugs, statins should be used judiciously in the appropriate patient population. The Advisory states that absolute contraindications to statins exist in patients with active or chronic liver disease and relative contraindications exist for patients taking specific concomitant medications (cyclosporin, gemfibrozil, high doses of niacin, macrolide antibiotics, various anti-fungal agents, and strong cytochrome P-450 inhibitors).

Various clinical definitions have been used for both myopathy and rhabdomyolysis [51]. Myopathy consists of muscle symptoms (pain, tenderness, or weakness) in conjunction with elevated serum creatine kinase levels (>10 x upper limit of normal or >1000 U/L). The estimated rate of myopathy with statin monotherapy is 0.025-0.5% and is dose-dependent [52]. The low doses of statins considered appropriate for OTC are associated with a very low rate of myopathy in the primary prevention population at intermediate risk for CHD [23]. The risk of myopathy increases with concurrent use of high dose statins with other drugs (especially strong Cytochrome P-450 3A4 inhibitors, such as cyclosporine, itraconazole, and erythromycin; or gemfibrozil) and is also increased with frailty, the very elderly, individuals with a smaller body mass index, and multisystem disease (e.g., chronic renal insufficiency associated with diabetes mellitus) [28]. Routine measurements of muscle enzymes contribute little to preventing the

[4] ZOCOR is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

possible development of myopathy [5; 53]. Myopathy can progress to rhabdomyolysis (typically defined as a CK>10,000 U/L in association with evidence of end organ damage, usually renal insufficiency). Severe rhabdomyolysis can result in acute renal failure and death [16].

Following the voluntary market withdrawal of cerivastatin (Baycol™, Bayer Pharmaceutical Division) in 2001, reevaluation of the safety of statins as a class, especially with respect to the effects of statins on skeletal muscle, was warranted. These safety concerns have recently been addressed in publications [5; 16; 53]. It appears that "the rate of fatal rhabdomyolysis for cerivastatin was far greater than that for other statins (16 to 80 times higher) [5]." More than 60% of the fatal cases with cerivastatin were associated with use of the highest dose (0.8 mg daily) [16]. A report by 3 FDA experts compared the rate of fatal rhabdomyolysis among different statins [16] (based on a detailed review of the FDA Adverse Event Reporting System), noted <1 death was reported per million prescriptions. There did not appear to be a difference in the rate of fatal complications among the 5 statins then available in the United States (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin). The report by these FDA experts concluded that the rates of severe myopathy should be considered as equivalent among all approved statins [16]. Furthermore, the rare progression to rhabdomyolysis is a dose-related adverse event much less likely to be seen with the 20 mg dose of lovastatin proposed for OTC use.

6.2 Hepatic Effects

Liver function test elevations associated with statin therapy are usually reversible with continued treatment, are dose-related, and may result from cholesterol lowering effects on hepatocyte cell membranes.

There are apparently 2 distinct and unrelated manifestations of statin-induced hepatic effects. The most common appears to be a self-limited, reversible, dose-related elevation of ALT that is asymptomatic. The other is rare reports of acute liver failure associated with all statins and may be due to an idiosyncratic reaction. Monitoring liver function tests for hepatotoxicity has not been effective in preventing or predicting serious liver disease, due to the rarity of this condition and the poor predictive value of minor ALT elevations [54].

7. The OTC Statin-Eligible Population

The proposed OTC Statin-Eligible Population defined through guidance from FDA and independent cardiologists is a primary prevention population with 2 or more risk factors and a 10% to 20% risk of CHD over 10 years without other underlying chronic conditions that complicate consumer self-management. Individuals with liver disease, LDL-C >170 mg/dL, the metabolic syndrome (as defined by triglycerides ≥200), diabetes, CHD, or history of stroke or other atherosclerotic cardiac disease are not candidates for OTC statins. Furthermore, the majority of individuals in this group should

be able to achieve ATP III target treatment goals (LDL-C<130 mg/dL) using a low-dose statin without the need for titration. Using data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994) and Year 2000 U.S. population information, Ford et al estimate that the Year 2000 U.S. population (ages 20 to 79 years) includes 23 million individuals without CHD or a CHD equivalent and who have 10-year risk for developing CHD in the 10% to 20% range. While there are challenges in creating an OTC label which captures this population exactly, it is possible to approximate this risk group through creative labeling. Additionally, it is believed that individuals with less than a 10% 10-year CHD risk may also benefit from a low dose statin. AFCAPS/TEXCAPS demonstrated benefit in a population with about 6% 10-year risk for CHD. The log-linear relation between cholesterol and risk reduction [31] also supports benefit in people with "average" LDL-C levels.

8. Current Use of OTC Cholesterol Lowering Agents

The general public is very interested in the treatment and prevention of CHD. Both health care surveys and the lay press reflect this interest. A variety of publications engage in detailed discussions on diet, coronary risk level, and prognosis for success in achieving LDL-C targeted goals. At least 25% of the adult population in the United States (57 to 65 million people) are concerned about their cholesterol and what to do about it [27]. Of these concerned consumers, 49% use a nonprescription nutriceutical product such as vitamin E (17%), garlic (15%), or niacin (8%). Red yeast rice imported from China actually contains a low dose of lovastatin, and the manufacturers claim it promotes healthy cholesterol levels [27]. As described in Table B-4, other products claiming a cardiovascular benefit are prominently advertised to consumers in a variety of media.

Table B-4

Dietary Supplements With Cardiovascular Claims

Product	Manufacturer	Putative Cholesterol Lowering Substance	Advertising Claims
Cholesterol Success™	Twinlab™	Plant sterols/stanols	"Clinically Proven." "Reduces Cholesterol up to 24%. May reduce the risk of heart disease."
Cholest-Aid Complete RX	PKI Nutrition , Inc.	Inositol hexanicotinate (the non-flush form of niacin)	"Powerful Support for the Cardiovascular System" "Promoting Good Heart Health." "If you are concerned about your cholesterol, ask for it by name!!" "Cholest-Aid Complete™ is a well-formulated, effective product containing clinically proven ingredients to support Cardiovascular health and normal Cholesterol levels." "This is a safe, well formulated product and addresses the whole range of cardiovascular health, not only helping to protect by balancing cholesterol levels of HDL & LDL and Triglycerides, but also helping to reduce homocysteine levels, helping to make arteries more elastic, and supporting antioxidant protection." Confirms Calin Pop, M.D., a physician Board-Certified in Internal Medicine"
Kyolic™ One Per Day	Wakunaga of America Co. Ltd.	Aged garlic extract	"Kyolic helps protect your heart by improving circulation, maintaining health levels of cholesterol…"†
Basikol	Health From The Sun	Plant sterols	"Cholesterol? These People Aren't Worrying About It!" "BASIKOL is an all-natural way to maintain healthy cholesterol levels without negative side effects."†
Lesstanol™ Policosanol	Swanson Health Products	Plant sterol	"Promotes healthy ratios of HDL to LDL cholesterol." †
Beta Sitosterol	Swanson Health Products	Sugar cane wax derivative	"A healthy choice for everyday cardiovascular maintenance, beta sitosterol is a powerful plant sterol that works naturally within the body to help promote a favorable lipid balance"†
† "These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease."			

[55]

OTC products directed toward the prevention of CHD are one of the fastest growing segment of health products [27]. The majority of dollars spent on such OTC "cholesterol lowering" agents involve garlic-containing products. Consumers spend billions of dollars per year on self-medication to prevent CHD, even though most of these products are of questionable benefit or efficacy [27].

Current options available to consumers to lower cholesterol are a poor substitute for a thoroughly studied pharmaceutical agent with proven efficacy and safety—especially from a public health perspective [56; 57; 58].

9. Statins as Nonprescription Drugs and the Public Health

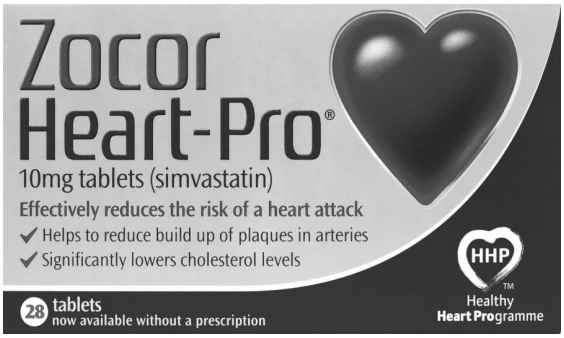
The availability of a statin without a prescription represents a logical next step in the prevention of atherosclerotic cardiovascular disease and is consistent with recommendations in the NCEP ATP III guidelines and the Institute of Medicine Quality Chasm Report, which recommends greater patient participation in their own healthcare [59; 60]. An over-the-counter statin such as MEVACOR™ OTC has potential to positively impact the public health.

Documented behavior by managed care organizations and drug reimbursement plans makes it extremely unlikely that an OTC statin will steer patients away from supervised medical care [61; 62]. Such concerns have been raised by various stakeholders that the availability of an OTC statin would allow managed care organizations to shift costs by forcing enrollees already on prescription statins or new patients to transfer therapy to the OTC statin. This concern has been addressed by an independent Towers Perrin study [63]. This study was conducted with leaders of 18 managed care companies from three payer segments to better understand their perspectives on the role of a low-dose statin for primary prevention of the intermediate risk population [23]. Findings of the study revealed that payer policies will continue to support access to prescription statins and no change in formulary status is to be expected should an OTC option become available.

Consumer surveys have shown that most patients will understand the limitations of an OTC drug for a chronic condition and realize whether or not they require the guidance of a physician [64]. In addition, the majority of patients are likely to discuss their use of an OTC drug with their primary medical doctor [65], especially if the medical condition persists. Furthermore, data from the CUSTOM Study (see Section G) demonstrate that the MEVACOR™ OTC Self-Management System will encourage consumer and physician interactions and steer appropriate consumers to supervised medical care, and when appropriate, prescription therapy. It is highly unlikely that patients who truly warrant prescription therapy will be relegated to lesser therapy by the availability of an OTC statin. The majority of consumers using OTC statins such as MEVACOR™ in conjunction with the MEVACOR™ Self-Management System have been shown to take responsibility for their cardiovascular health and assume greater control over their medical decisions - either remaining on the OTC statin or returning to their primary medical doctor in order to transition to a prescription lipid-lowering agent.

Cost shifting and reimbursement are issues that now require consideration with any Rx-to-OTC switch. However, many Americans pay for their medications without the benefit of a drug reimbursement plan or have significant co-pay despite such a plan. Ultimately, OTC statins are likely to demonstrate cost-effectiveness based on savings of both indirect and direct costs. "Adding the indirect cardiovascular disease costs associated with productivity losses at work and home can result in forecasted cost savings to society as a whole such that lipid therapy could potentially save lives and money" for the primary prevention of cardiovascular disease [66].

10. The OTC Paradigm of ZOCOR™ in the United Kingdom (UK)



Front panel of Zocor Heart-Pro

Facing a serious public health issue with cardiovascular mortality on the rise, in July 2004 the Medicines and Healthcare Products Regulatory Agency (MHRA) approved the switch of ZOCOR™ (simvastatin) 10 mg from POM (Prescription Only Medicine) to P (Pharmacy) classification in the United Kingdom. The product is now being marketed under the brand name "Zocor Heart-Pro."

Under Category P, Zocor Heart-Pro is available directly from the pharmacist without a physician's prescription. Pharmacists and their staff are trained to assist consumers in appropriately choosing Zocor Heart-Pro as an initial purchase, as well as making repeat purchase decisions for continued use. Support materials are provided to assist pharmacy staff in helping consumers determine if Zocor Heart-Pro is appropriate, including a checklist for assessing a consumer's level of risk for CHD; informational materials on CHD and CHD major risk factors; detailed information on simvastatin; information on other interventions to reduce the risk of CHD; and specific advice for individuals making repeat purchases. See Appendix J for some examples of these support materials.

The intention is to make Zocor Heart-Pro available to those individuals who are at a moderate risk (10% 10-year risk) of CHD. The guidelines to pharmacists recommend Zocor Heart-Pro for: men 55 years or more, who are likely to be at moderate risk of CHD; and men 45-54 years and women over 55 years, who are likely to be at moderate risk for developing CHD if they have one or more CHD risk factors. Risk factors include family history of CHD, smoker, overweight, and/or south Asian ethnicity. Pre-purchase cholesterol testing is not required and liver function monitoring is not required.

The reclassification of simvastatin 10 mg from POM to P, and the resulting increased access, is expected to have many positive effects for the public. Zocor Heart-Pro Heart Healthy Program is providing a comprehensive cholesterol-lowering system that helps address a serious public health problem in the UK. Many of the system's features have been tested in the MEVACOR™ OTC development program and are, in fact, now being used in the marketplace in the UK.

11. Conclusions

The OTC Statin-Eligible Population is at significant risk for the future development of coronary heart disease. This population is eligible for therapy with statins based on current guidelines. Despite this, a substantial cholesterol treatment gap for treating and preventing coronary heart disease exists in the present healthcare system. The Institute of Medicine has suggested a redesign of the shortcomings of our current health care system that also helps address this Cholesterol Treatment Gap. The availability of the MEVACOR™ OTC Self-Management System would be entirely consistent with the design and intent of the IOM's healthcare redesign. The MEVACOR™ OTC Self Management System has a potential to enhance the public health by helping to reduce extraordinarily high levels of morbidity and mortality from atherosclerotic cardiovascular disease and the associated direct and indirect societal costs. Lovastatin is particularly suited for primary prevention in the OTC population because of its many years of clinical experience demonstrating its proven benefit in primary prevention as well as its proven safety record. Furthermore, the MEVACOR™ OTC Self-Management System targets the appropriate population and encourages a partnership with health care professionals in managing CHD risk.

C. EFFICACY AND BENEFIT OF LOVASTATIN

1. Rationale for the Lovastatin 20 mg Dose

Lovastatin 20 mg has been well studied in 2 large-scale, long-term, randomized, placebo-controlled clinical trials comprising almost 15,000 patients. Efficacy was evaluated in two important and distinct ways. The first was an assessment of the effects of lovastatin on the lipid profile and individual lipoprotein levels. The second was on clinical outcomes associated with coronary heart disease (CHD). Changes in lipid profile and lipoprotein levels are surrogates for clinical outcomes; and as such represent short-term indicators of potential long-term effects. The effects of lovastatin on lipid profile were assessed in the Expanded Clinical Evaluation of Lovastatin (EXCEL) Study [13] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [7]. EXCEL (conducted Jul-1987 to Jul-1989), evaluated the efficacy and safety of lovastatin with focus on changes in the lipid profile. AFCAPS/TexCAPS (conducted May-1990 to Sep-1997) evaluated the lipid modifying effects of lovastatin on clinical outcomes. Results from AFCAPS/TexCAPS have shown lovastatin (including lovastatin 20 mg once daily) to reduce the risk of first acute major coronary events by 37%.

2. Key Clinical Trials

2.1 EXCEL (The Expanded Clinical Evaluation of Lovastatin Study)

2.1.1 Study Design

The Expanded Clinical Evaluation of Lovastatin Study (EXCEL) was a 362-site multimember, randomized, double-blind, placebo-controlled study with 5 parallel treatment groups. The treatment groups were lovastatin 20 mg every evening, 40 mg every evening, 20 mg twice a day, 40 mg twice a day, and placebo. A 4- to 6-week diet-only run-in baseline period was followed by a 48-week diet and active treatment period.

2.1.2 Efficacy Results

A distinct dose response occurred for all plasma lipids (results are summarized in Table C-1). The 20 mg once daily dose of lovastatin produced a 24% reduction in LDL-C after 48 weeks of treatment.

The proportion of patients who achieved an LDL-C <130 mg/dL after 48 weeks of treatment increased as daily doses of lovastatin increased.

Table C-1 presents the LDL-C data for all patients distributed by the five categories required for the all-patients-treated (scored dropouts) analysis.

Table C-1

Effects of Lovastatin on Lipid Levels in the EXCEL Study Week 12-48

Mean % Change From Baseline	Placebo (n=1663)	Lovastatin			
		20 mg/evening (n=1642)	40 mg/evening (n=1645)	20 mg twice/day (n=1646)	40 mg twice/day (n=1649)
Total-C	0.7	-17	-22	-24	-29
LDL-C (mg/dL)	0.4	-24	-30	-34	-40
HDL-C (mg/dL)	2.0	6.6	7.2	8.6	9.5
Total-C/HDL-C ratio	0.6	-21	-26	-29	-34

2.2 AFCAPS/TexCAPS (The Air Force/Texas Coronary Atherosclerosis Prevention Study)

2.2.1 Study Design

This was a randomized, double-blind, placebo-controlled study occurring in 2 clinical locations in the United States (San Antonio and Fort Worth, Texas). The objective of the study was to compare lovastatin with placebo for prevention of the first acute major coronary even in men and women without clinically evident atherosclerotic cardiovascular disease with average total cholesterol (TC) and LDL-C levels and below-average high density lipoprotein cholesterol (HDL-C) levels. A pretreatment 12-week diet period including a 2-week placebo run-in occurred, followed by a median treatment period of 5.1 years (range 1 month to 7.2 years). Therapy was initiated with lovastatin 20 mg or placebo. Participants with an LDL-C >110 mg/dL (average of Weeks 6 and 12) were titrated to 40 mg (two 20-mg tablets) at Week 18. Participants were seen every 6 weeks for the first 48 weeks of the treatment period followed by visits at Week 60, Month 18, and every 6 months thereafter.

Men aged 45 to 73 years and postmenopausal women aged 55 to 73 years who met the lipid entrance criteria and had no prior history, signs, or symptoms of definite myocardial infarction, angina, claudication, cerebrovascular accident, or transient ischemic attack were eligible for participation in the study. Lipid entry criteria (TC 180-264 mg/dL; LDL-C 130-190 mg/dL; HDL-C 45 mg/dL for men or 47 mg/dL for women; and triglycerides 400 mg/dL) were to be met at both 4 and 2 weeks prior to randomization, with less than 15% difference in LDL-C values. In addition, participants with LDL-C between 125-129 mg/dL were included when the ratio of TC to HDL-C was more than 6.0. Volunteers with uncontrolled hypertension, secondary hyperlipidemia, or type 1 or type 2 diabetes mellitus that was either managed with insulin or associated with glycohemoglobin level of at least 10% (20% above the upper limit of normal) were excluded. Additionally, volunteers were excluded if, according to the 1983 Metropolitan Life Insurance tables, they had a body weight more than 50% greater than the desirable limit for height. All participants provided written informed consent.

2.2.2 Efficacy Results

The lovastatin treatment group had LDL-C reduced by 25% and increased HDL-C by 6%. Survival analyses revealed significant and clinically important differences between treatment groups in the primary and secondary efficacy endpoints. Compared with placebo, lovastatin reduced the risk of experiencing a first acute major coronary event by 37% ($p<0.001$). A summary of all endpoints and the relative risk reductions achieved with lovastatin is shown in Table C-2.

Table C-2

Summary of Endpoints and Relative Risk Reduction
(AFCAPS/TEXCAPS study)

Endpoint	Lovastatin† N (%)	Placebo† N (%)	Between Treatment p-Value‡	Relative Risk§ (95% CI)
Primary endpoint	116 (4.0)	183 (6.8)	<0.001§	0.63 (0.50, 0.79)
Secondary endpoints				
Revascularization	106 (3.8)	157 (5.9)	0.001	0.67 (0.52, 0.85)
Unstable angina	60 (2.0)	87 (3.1)	0.023	0.68 (0.49, 0.95)
Fatal and nonfatal MI	57 (1.9)	95 (3.7)	0.002	0.60 (0.43, 0.83)
Fatal and nonfatal cardiovascular events	194 (6.8)	255 (9.3)	0.003	0.75 (0.62, 0.91)
Fatal and nonfatal coronary events	163 (5.8)	215 (7.9)	0.006	0.75 (0.61, 0.92)

† Percents are the cumulative incidence from unstratified lifetable model.
‡ Log-rank statistic, stratified by study center and gender.
§ Adjusted for the interim analysis.

2.2.3 Primary Endpoint

The primary endpoint in AFCAPS/TexCAPS was time to first occurrence of sudden cardiac death, fatal or nonfatal MI, or unstable angina. Individually and together these predefined events comprise and define the composite primary endpoint "acute major coronary events." Of the 299 participants with primary endpoints, there were 116 participants with endpoints in the lovastatin group and 183 in the placebo group. Approximately 45% of the primary endpoints were due to new onset unstable angina while 49% were due to MI. The remainder was classified as sudden cardiac death.

The data were also examined using a Cox proportional hazards model. The proportionality assumption for treatment group was tested and found appropriate ($p=0.576$). This implies that the relative risk was constant over time and also means that absolute risk diverged over time. The relative risk for the lovastatin group compared

with the placebo group estimated with this model was 0.63 with a 95% CI of (0.50, 0.79); p<0.001. The risk reduction in the lovastatin group relative to the placebo group, which is equal to 100 times the complement of the relative risk, therefore, was calculated to be 37% with a 95% CI of (21, 50%). Kaplan-Meier estimates indicate that one would need to treat 110 participants for 3 years, 74 participants for 4 years, 53 participants for 5 years, or 38 participants for ~73 months (which is the end of follow-up but while at least 500 participants are still at risk in each treatment group), in order to prevent a first primary endpoint event. Alternately, if one treated 1,000 participants for 5 years, ~19 participants would be prevented from having a first primary endpoint event. Using crude rates for the 3304 participants in the lovastatin group, there were 116 with primary endpoints during 17,041 person-years at risk (PYR) of follow-up. For the 3301 participants in the placebo group, there were 183 with primary endpoints during the 16,865 PYR of follow-up.

Risk factors that significantly affected the outcome for the primary endpoint included treatment, gender, age, history of hypertension, family history of CHD, smoking, baseline LDL-C and baseline HDL-C. Results from a Cox proportional hazards model that includes the above factors, indicate a 39% reduction in risk for participants treated with lovastatin compared with placebo, ~3.4 times the risk for men compared with women, a 35% increase in risk for every 5 years of age, a 67% increase in risk for hypertensives, a 57% increase in risk for those with a family history of CHD, an 88% increase in risk for smokers, a 0.8% increase in risk for every 1 mg/dL increase in baseline LDL-C, and a 2.7% reduction in risk for every 1 mg/dL increase in baseline HDL-C.

The risk reduction was significant and comparable to the overall group of study participants within the following subgroups: men (p<0.001), younger participants (p=0.002), older participants (p=0.011), smokers (p=0.002), nonsmokers (p=0.002), nondiabetics (p<0.001), hypertensives (p=0.016), and nonhypertensives (0.002). Risk reductions of comparable magnitude to the overall group of study participants were noted among women and diabetics; however, the small number of events in these subgroups did not allow a conclusion of statistical significance. Event rates were higher in diabetics as would be expected; however, there were only 155 diabetics in the study so that this factor was not significantly associated with the primary endpoint (p=0.335) (See Table C-3).

Table C-3

Effect of Treatment Within Subgroups at Risk
(AFCAPS/TEXCAPS study)

Subgroup at Risk	Treatment Group	n	Cases	Relative Risk (95% CI)[†]
Men	Lovastatin	2805	109	0.63 (0.50, 0,81)
	Placebo	2803	170	
Women	Lovastatin	499	7	0.54 (0.22, 1.36)
	Placebo	498	13	
Age ≤median[‡]	Lovastatin	1712	38	0.53 (0.36, 0.79)
	Placebo	1713	71	
Age ≥median[‡]	Lovastatin	1592	78	0.69 (0.51, 0.92)
	Placebo	1588	112	
Smokers	Lovastatin	429	17	0.41 (0.23, 0.73)
	Placebo	389	36	
Nonsmokers	Lovastatin	2875	99	0.67 (0.52, 0.87)
	Placebo	2912	147	
Diabetics	Lovastatin	84	4	0.63 (0.17, 2.30)
	Placebo	71	6	
Nondiabetics	Lovastatin	3220	112	0.63(0.50, 0.80)
	Placebo	3230	177	
Hypertensives	Lovastatin	719	38	0.61 (0.41, 0.91)
	Placebo	729	62	
Nonhypertensives	Lovastatin	2585	78	0.64 (0.48, 0.85)
	Placebo	2572	121	

[†] Cox proportional hazard model, stratified by study center and gender, except for gender subgroups where model is stratified by study center.
[‡] Median for each gender, 57 years for men, 62 years for women.

Table C-4 summarizes treatment by category of LDL-C. The majority of the AFCAPS/TexCAPS participants had baseline LDL-C levels in the range of 130 to <160 mg/dL. Approximately 88% of participants had LDL-C between 130 to 190 mg/dL. Subgroup analyses were performed for participants with <2 risk factors and ≥2 risk factors and for participants in the baseline LDL-C categories. Because there were relatively few participants with a baseline LDL-C ≥190 mg/dL, they were pooled with participants with a baseline LDL-C between 160 and 190 mg/dL.

Table C-4

Number (%) of Participants by Baseline LDL-C Category
(AFCAPS/TEXCAPS study)

LDL-C Category	Lovastatin n (%)	Placebo n (%)
<130 mg/dL	348 (10.5)	343 (10.4)
130 to <160 mg/dL	2054 (62.2)	2038 (61.7)
160 to <190 mg/dL	860 (26.0)	878 (26.6)
≥190 mg/dL	42 (1.3)	42 (1.3)

2.2.4 Secondary Endpoints

Secondary endpoints investigated whether chronic treatment with lovastatin compared with placebo would decrease the rates of: (1) fatal and nonfatal coronary revascularization procedures; (2) new onset unstable angina; (3) fatal and nonfatal MI's; (4) fatal and nonfatal cardiovascular events; (5) fatal and nonfatal coronary events; (6) cardiovascular mortality; and (7) CHD mortality. The numbers of CVD or CHD deaths did not meet the pre-specified criterion for statistical comparison (i.e., ≥66 events, 1% of the entire sample size). Forty-two participants had a fatal cardiovascular event, 17 in the lovastatin group and 25 in the placebo group. Twenty-six participants had a fatal CHD event, 11 in the lovastatin group and 15 in the placebo group. Results for the secondary endpoints are summarized in Table C-2.

2.2.5 Lipid Parameters

Changes in lipid parameters from baseline to Week 18 were analyzed (see Tables C-5 and C-6). Differences between groups were significant ($p<0.001$) for all the lipid parameters. Most within-group changes were significant as well in both treatment groups. There were mean differences between lovastatin and placebo of –26.5% in LDL-C, -19.3% in TC, 4.8% in HDL-C, -12.7% in median TG, -29.6% in the LDL-HDL-C ratio, and -23.5% in the TC/HDL-C ratio.

Such changes represent the effect of treatment with lovastatin 20 mg alone, since titration to 40 mg did not occur until after week 18. Thus, based on this data, lovastatin 20 mg led to a mean 24% reduction in LDL-C from baseline with 82.1% of participants achieving the ATP III designated target goal of LDL-C<130 mg/dL.

Table C-5

Summary Statistics—Percent Change From Baseline for Lovastatin 20 mg (AFCAPS/TEXCAPS)

	Week 18 % Change
Total-C (mg/dL)	
N	2276
Mean ± SD	-16.9±9.0
Median	-17.2
Q1,Q3	-22.9, -11.4
LDL-C (mg/dL)	
N	2276
Mean ± SD	-24.3±12.1
Median	-25.1
Q1,Q3	-32.1, -17.0
HDL-C (mg/dL)	
N	2276
Mean ± SD	8.2±15.6
Median	7.0
Q1,Q3	-1.4,16.7
TC/HDL Ratio	
N	2276
Mean ± SD	-22.2±12.9
Median	-23.2
Q1,Q3	-30.3, -15.4

Table C-6

Percent of Patients Reaching Goal at Week 18 With Lovastatin 20 mg (AFCAPS/TEXCAPS)

	Goal	Lovastatin 20 mg (N=1292)
TOTAL-C		
	≥20% reduction	36.8
	≥10% reduction	79.8
	<200 mg/dL	81.0
LDL-C		
	≥20% reduction	67.9
	≥10% reduction	88.6
	<100 mg/dL	21.5
	<130 mg/dL	82.1

2.2.6 Benefit of Lovastatin 20 mg Once Daily in the Proposed OTC Population

An analysis was designed to estimate the impact of treatment with 20 mg lovastatin in lowering the risk for a first acute major CHD event among the MEVACOR™ OTC eligible population using data from AFCAPS/TexCAPS. Although 75% of the AFCAPS/TexCAPS participants were intermediate risk according to ATP III guidelines, only 44% of participants would have been eligible for MEVACOR™ OTC by the proposed label.

The proposed MEVACOR™ OTC label-eligible population consists of individuals who meet all of the following criteria:

1. Male ≥45 years or female ≥55 years;
2. LDL-C 130 to 170 mg/dL;
3. Has one or more of the following risk factors:
   a. Current smoker;
   b. HDL-C <40 mg/dL
   c. Positive family history (father and/or brother who had a heart attack or angina before the age of 55 years, or mother and/or sister who had a heart attack or angina before 65 years of age); or
   d. High blood pressure; and

4. Does not have any of the following conditions:
   a. Current liver disease;
   b. History of muscle pain, weakness, and/or tenderness from taking cholesterol lowering medication;
   c. Pregnant or breast-feeding; and
   d. Allergy to lovastatin.

Based on ATP III guidelines, target LDL-C for the MEVACOR™ OTC eligible population should be <130 mg/dL. Because lovastatin titration in AFCAPS/TexCAPS was triggered by an LDL-C target goal that is lower than the current ATP III goal, direct estimation of the benefit of 20 mg in the MEVACOR™ OTC setting is not possible using AFCAPS/TexCAPS. To assess the impact of treatment with 20 mg of lovastatin in lowering the risk for developing CHD events in those who meet the proposed MEVACOR™ OTC label criteria, the benefit of lovastatin among specific subgroups of AFCAPS\TexCAPS participants was estimated. Three subgroups were selected for analysis: all MEVACOR™ OTC-eligible participants, MEVACOR™ OTC-eligible participants who remained on 20 mg of lovastatin throughout the trial, and MEVACOR™ OTC-eligible participants who met the LDL-C target goal of <130 mg/dL by Week 6.

2.2.7 Risk Assessment

The absolute and relative risk of a CHD event among MEVACOR™ OTC-eligible participants and each of the additional subgroups was assessed. The absolute risk of a CHD event was estimated two different ways: using the crude event rate over the trial period and the Kaplan-Meier event rate estimated over a period of 6 years [67]. The crude observed event rate is the number of events divided by the total person-years for each treatment group. Because not all patients had complete follow-up information, the event rate using the Kaplan-Meier survival method was used as well. In addition, an estimate of the relative risk for participants treated with lovastatin compared with placebo was based on the Cox Proportional Hazards model with gender and site included as stratification variables [68].

Participant Characteristics

Baseline information on participant characteristics is summarized in Table C-7 for all patients in AFCAPS\TexCAPS as well as for those patients who would be eligible for 20 mg of lovastatin according to the proposed MEVACOR™ OTC product label. The table includes baseline information on gender, age, race, total cholesterol, LDL-cholesterol, HDL-cholesterol, systolic blood pressure, diastolic blood pressure, hypertension status, smoking status, diabetes status, and family history of CHD (through sibling or parents) as well as estimates of 10-year risk for CHD (based on the Framingham risk score) and 10-year risk for hard CHD [22]. Overall, the participant characteristics of the entire AFCAPS/TexCAPS cohort are very similar to the characteristics of the MEVACOR™ OTC-eligible subgroup. However, the proportion of males, the proportion of smokers, and the proportion of those with a family history of

CHD are slightly higher in the MEVACOR™ OTC-eligible population. In both cohorts, the treatment groups are quite similar in terms of their baseline characteristics. For both the entire AFCAPS\TexCAPS cohort and the MEVACOR™ OTC-eligible subgroup, t-tests determined that there was not a significant difference in the mean cholesterol levels and blood pressure measurements between those randomized to the lovastatin and placebo treatment groups. Similarly, the chi-square test established that there was not a significant difference in the classification of participants according to gender, race, hypertension status, smoking status, and family history of CHD.

Table C-7

Mean Baseline Participant Characteristics—
Entire AFCAPS/TexCAPS Cohort Versus MEVACOR™ OTC Eligible Participants

	AFCAPS		MEVACOR™ OTC Label-Eligible	
	Lova (n=3304)	Pbo (n=3301)	Lova (n=1433)	Pbo (n=1449)
Male (%)	84.9	84.9	87.2	88.4
Age (yrs)	58.2	58.1	58.5	58.1
Cholesterol (mg/dL)				
Total-C	220.8	220.8	213.1	213.7
LDL-C	150.2	150.5	148.9	149.4
HDL-C	36.9	37.0	36.3	36.3
Total-C/HDL-C ratio	6.1	6.1	6.0	6.0
Blood Pressure (mm Hg)				
Systolic	138.3	138.1	138.6	138.2
Diastolic	77.8	77.8	77.7	78.0
HTN (%)	21.8	22.1	25.6	25.5
HTN Rx (%)	20.0	21.1	23.2	24.7
Smoker (%)	13.0	11.8	16.3	14.8
Family history (%)	15.0	16.3	18.5	19.8
Framingham 10-year risk (%)				
Equation w/SBP	18.4	18.2	18.5	18.2
Equation w/DBP	16.5	16.4	16.5	16.4
ATP III 10-yr risk (%)	13.8	13.5	14.3	14.1

Crude Observed and Kaplan-Meier Event Rates

The risk of a coronary heart disease event (defined as the AFCAPS/TexCAPS primary outcome composite endpoint of sudden cardiac death, fatal or nonfatal myocardial infarction, or unstable angina) was first assessed using the crude observed event rates. For the AFCAPS/TexCAPS cohort, the average amount of follow-up time available for participants randomized to the lovastatin and placebo groups, respectively, was 5.15 years and 5.10 years. The maximum amount of follow-up time for each treatment group was ~7.25 years. For each of the subgroup analyses, the average and maximum follow-up times for both treatment groups were very similar, compared to the entire AFCAPS cohort.

Table C-8 gives the observed event rate per 1000 patient years at risk (number of events/total follow-up time x 1000) and 6-year Kaplan-Meier event rates. For each of the subgroup analyses, the event rate for participants randomized to the lovastatin treatment group was lower than the event rate for participants in the placebo subgroup.

The number needed to treat (NNT) (to prevent one CHD event) based on the Kaplan-Meier estimates following 6 years of treatment is 34, 25, 16, and 28 for All AFCAPS/TexCAPS Participants, the MEVACOR OTC Label-Eligible Participants, the Non-Titrators, and the MEVACOR™ OTC Label-Eligible Participants that Achieved the MEVACOR™ OTC Label Goal (LDL-C<130 mg/dL) at Week 6, respectively. The NNT for non-titrating participants treated with lovastatin 20 mg following 6 years of treatment is generally similar to the NNT's for the other subpopulations and for the overall AFCAPS/TexCAPS population.

Table C-8

Observed Versus Kaplan-Meier Event Rates for Each Subgroup by Treatment
(AFCAPS/TexCAPS Study)

	N	No. of Events	Total Person Years of Follow-Up	Observed Event Rate (per 1000 Patient Years at Risk)	KM Event Rate (Per Patient Over 6 Years)	Number Needed to Treat‡
All AFCAPS/TexCAPS Participants						
Lovastatin	3304	116	17011	6.82	0.0383	34
Placebo	3301	184	16834	10.93	0.0678	
Mevacor™ OTC-Eligible Participants						
Lovastatin	1433	48	7431	6.46	0.0347	25
Placebo	1449	88	7371	11.94	0.0748	
Non-Titrators						
Lovastatin	775	23	3960	5.81	0.0301	16
Placebo†	775	48	4018	11.95	0.0958	
To Reach OTC-Goal of LDL-C <130 mg/dL at week 6						
Lovastatin	1259	42	6527	6.44	0.0354	28
Placebo†	1259	78	6431	12.13	0.0724	

† Refers to the matched set of placebo participants.
‡ The number needed to treat to avoid one CHD event was calculated using the Kaplan-Meier event rate estimated over a period of 6 years.

The Kaplan-Meier survival curves in Figures C-1, C-2, and C-3 give the Kaplan-Meier survival curves for both the entire AFCAPS\TexCAPS cohort and the MEVACOR™ OTC-eligible subgroup for each treatment group. From the plots it is apparent that the MEVACOR™ OTC-eligible subgroup has very similar Kaplan-Meier survival estimates as the entire AFCAPS\TexCAPS cohort. It is also clear that participants in the lovastatin group tended to have lower event rates than their counterparts in the placebo group. The difference in their survival curves appears to become more distinct over time.

Figure C-1

Kaplan-Meier Curves for Probability of Avoiding a CHD Event:
Entire AFCAPS/TexCAPS Population on Lovastatin (20 and 40 mg) Versus Placebo and MEVACOR™ OTC Label-Eligible Participant

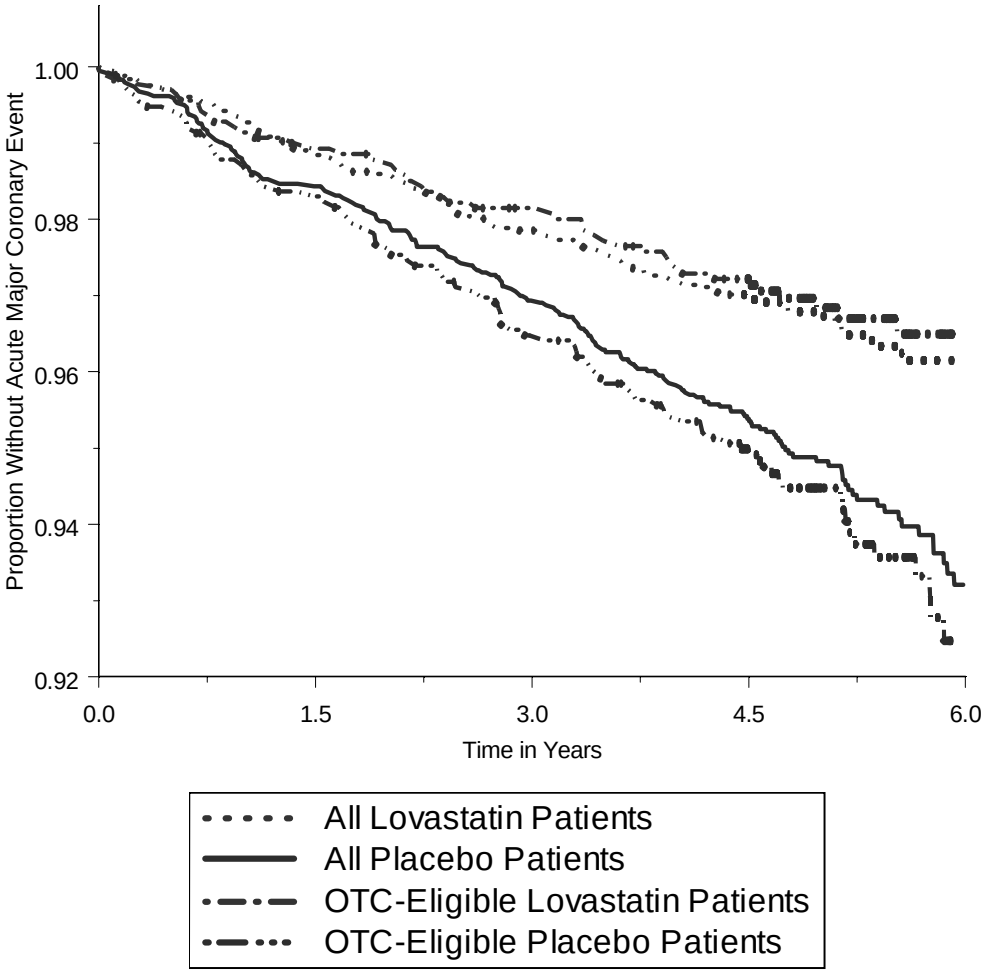


Figure C-2

Kaplan-Meier Curves for Probability of Avoiding a CHD Event:
MEVACOR™ OTC Label-Eligible Participants and Non-Titrators on Lovastatin 20 mg
Versus MEVACOR™ OTC Matched Non-Titrator Placebo Population Participants and
MEVACOR™ OTC Label-Eligible Participants Versus Matched Placebo Group

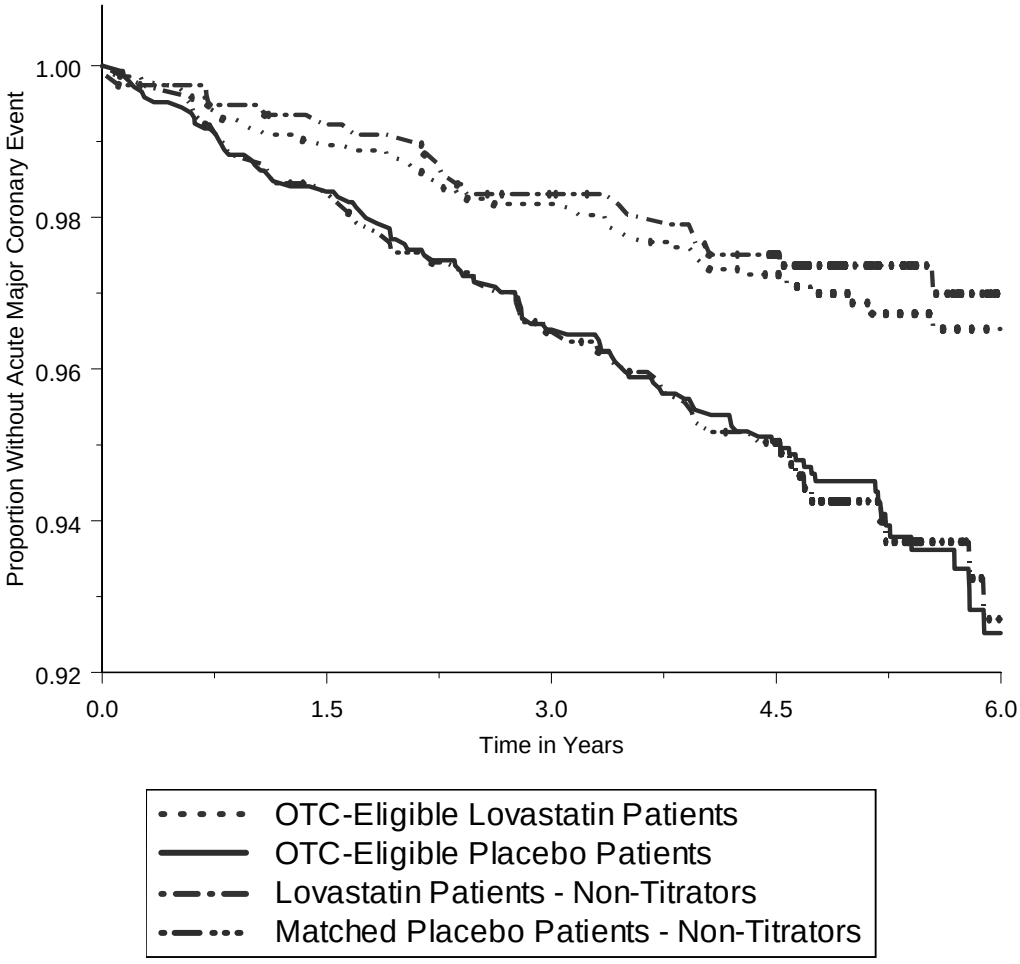
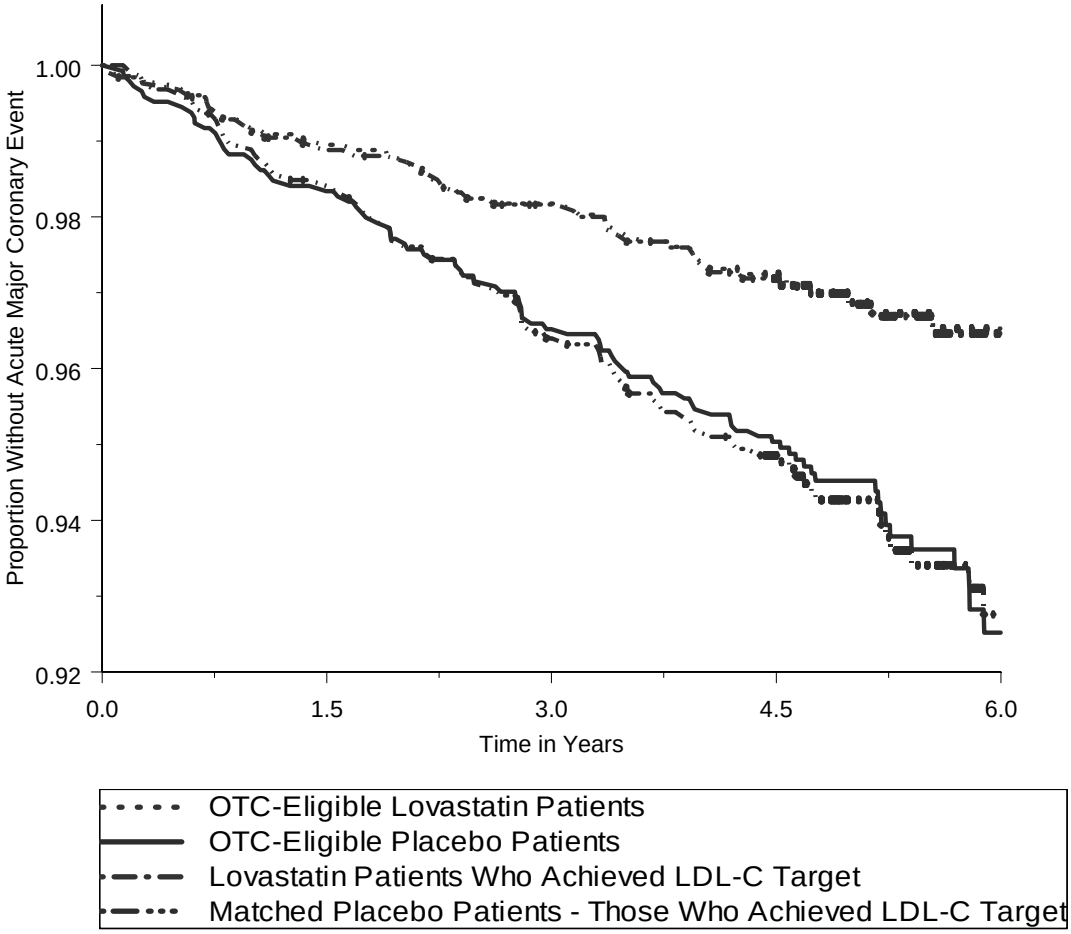


Figure C-3

Kaplan-Meier Curves for Probability of Avoiding a CHD Event:
MEVACOR™ OTC Label-Eligible Participants on Lovastatin 20/40 mg that Reached LDL-C target Goal (<130 mg/dL) Versus MEVACOR™ OTC Matched Placebo Population and MEVACOR™ OTC Label-Eligible Lovastatin Participants Versus MEVACOR™ OTC Label-Eligible Placebo Group

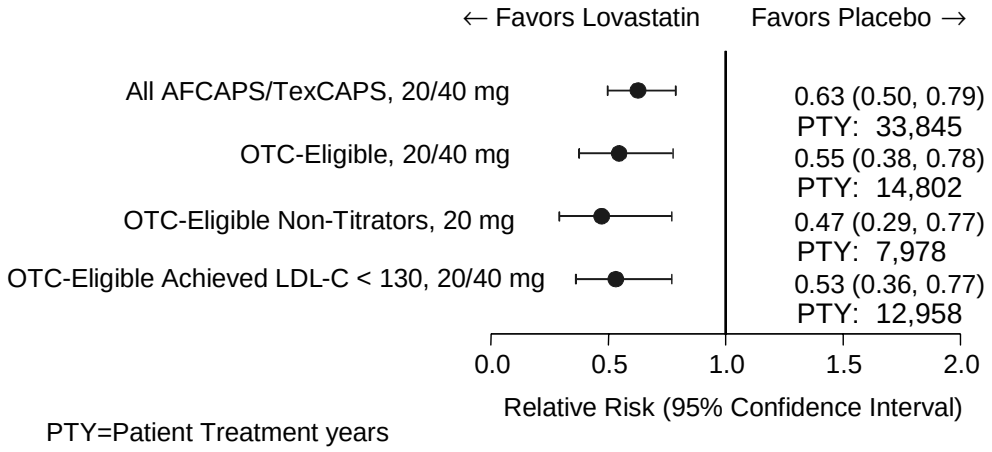


Figures C-2 and C-3 illustrate the Kaplan-Meier survival curves for each of the subgroup analyses versus the MEVACOR™ OTC-eligible cohort. These plots indicate that the Kaplan-Meier event rates for the placebo subgroups are much higher (lower probability of being CHD free) than the event rates for participants randomized to the lovastatin treatment group. Similar to the results that were given before, this difference does not appear to dampen over time.

The relative risk estimates and their 95% confidence intervals based on the Cox Proportional Hazards model are given in Figure C-4. The p-value for the test of significance is also given. The results indicate that there is a significant difference in the risk estimates of those in the lovastatin treatment subgroups as compared to those in the matched set of placebo participants. The risk ratios indicate that those in the lovastatin treatment subgroups are at a significantly lower risk of having a CHD event as their placebo counterparts.

Figure C-4

Relative Risk Ratio Based on Cox Proportional Hazards Model
By AFCAPS/TexCAPS Subgroup



PTY=Patient Treatment years

2.2.8 Summary of AFCAPS/TexCAPS Results for 20 mg Lovastatin With OTC-Eligible Population

This analysis was designed to estimate the impact of treatment with 20 mg of lovastatin in lowering the risk for developing a primary CHD event in the MEVACOR™ OTC label-eligible population using data from AFCAPS/TexCAPS. The analysis compared the risk of developing a CHD event in those who would have been recommended for treatment according to the proposed MEVACOR™ OTC label between patients randomized to the lovastatin group to those randomized to the placebo group. Also analyzed were 2 additional subgroups: participants who remained on 20 mg of lovastatin and participants randomized to lovastatin who achieved the ATP III (and proposed MEVACOR™ OTC label) LDL-C target goal (<130 mg/dL). Each of these additional subgroups, were compared to a set of matched placebo patients. The results of each of these subgroup analyses indicate that treatment with lovastatin (and lovastatin 20 mg in particular) significantly reduces the risk of a CHD event.

2.3 CUSTOM (A Consumer Use Study of OTC MEVACOR™)

2.3.1 Study Design

CUSTOM was an open-label, uncontrolled, "all-comers," 26-week duration, multicenter, actual use study conducted to observe consumer self-selection and de-selection behavior in a naturalistic OTC setting. The design and results of CUSTOM are described in detail in the Consumer Behavior section of this document (see Section G). The study was primarily designed to observe consumer initial use decisions to purchase MEVACOR™ OTC (self-selection behavior) and consumer continued use decisions (de-selection behavior) in a naturalistic OTC setting. Drug efficacy was a secondary objective.

2.3.2 Efficacy Results

Efficacy of non-prescription lovastatin 20 mg in CUSTOM was evaluated by the percentage change from baseline of LDL-C and the numbers of Users (participants who took at least one dose of study drug) achieving LDL-C goal of <130 mg/dL at the end of the study. Participants were instructed by labeling to fast before having lipid levels checked and results have been subsetted according to whether or not fasting occurred at the pre- and post-drug timings.

Change From Baseline

Data summarizing available information about percent change from baseline in cholesterol values is summarized in Table C-9. Additional details concerning the data for LDL-C are presented in Table C-10. The median and other quartiles (25^{th} and 75^{th}) have been used to summarize the data due to the presence of unusually large values of percent change for LDL-C. The median is less sensitive to unusually large values than is the mean. The interquartile range (the difference between the 75^{th} and 25^{th} percentiles) can be used as a robust measure of variation. The median reduction in LDL-C achieved in the population who used MEVACOR™ OTC was 20.6%. A larger reduction, 25.2%, was observed in the subgroup of 243 Users that fasted at baseline and end of study.

Table C-9

Summary of LDL-C, HDL-C, and Total Cholesterol—CUSTOM Study
(Users With Laboratory Reported Cholesterol Values)[†]

	Low Density Lipoprotein (LDL-C)			High Density Lipoprotein (HDL)			Total Cholesterol		
	N	Median (mg/dL)	25^{th}, 75^{th} Percentiles	N	Median (mg/dL)	25^{th}, 75^{th} Percentiles	N	Median (mg/dL)	25^{th}, 75^{th} Percentiles
Baseline	931	155	132, 180	1015	45	37, 55	1053	243	218, 271
End of study	878	120	100, 144	932	45	37, 54	962	204	179, 232
% change from baseline[‡]	811	-20.6	-34.4, -5.0	906	0	-9.5, 10.0	957	-14.6	-24.9, -4.6

[†] Includes fasting and non-fasting Users.

[‡] 100 (Cholesterol value at final follow-up visit - Cholesterol value at baseline)/Cholesterol value at baseline).

Table C-10

Summary of LDL Cholesterol by Fasting Status—CUSTOM Study
(Users With Laboratory Reported LDL-C Values)

	Fasting Status†	N	Median (mg/dL)	25th, 75th Percentiles
Baseline (n= 931)	Fasted	378	165	142, 188
	Not fasted	551	146	126, 173
	Unknown	2	198	NA
End of study (n= 878)	Fasted	608	118	100, 142
	Not fasted	267	122	102, 148
	Unknown	3	133	NA
% Change from baseline (n= 811)	FF	243	-25.2	-38.4, -9.0
	NF	324	-19.7	-32.4, -3.3
	FN	83	-20.7	-37.7, -8.8
	NN	156	-16.5	-32.2, 2.2
	Unknown	5	-25.8	NA

† FF indicates participants fasted at both the baseline and End of Study, NF indicates participants did not fast at baseline and fasted at End of Study, FN indicates participants fasted at baseline and did not fast at End of Study, NN indicates that participants did not fast at either time point (i.e., Baseline or End of Study).
NA indicates insufficient sample size to report 25th and 75th percentiles.
Unknown indicates the information is not known for at least one of the time points.

Users Who Achieved LDL-C Goal

The distribution of the 1059 Users by baseline LDL-C and end of study LDL-C is presented in Table C-11. Of the 878 Users with a known LDL-C value at the end of the study, 548 (62.4%) were at the LDL-C goal level of <130 mg/dL.

Table C-11

Counts of LDL-C Results
Baseline Versus End of Study—CUSTOM Study (Users)

	End of Study						
Baseline	<100	100 to 129	130 to 159	160 to 170	>170	Unknown	Total
<100	38	17	3	0	1	6	65
100 to 129	47	58	26	1	2	10	144
130 to 159	69	123	54	10	10	44	310
160 to 170	10	31	22	10	7	15	95
>170	28	88	84	22	50	45	317
Unknown	16	23	16	6	6	61	128
Total	208	340	205	49	76	181	1059

3. Discussion of Lovastatin Efficacy

The efficacy of lovastatin has been evaluated in two large-scale, long-term, randomized, placebo-controlled clinical trials, EXCEL and AFCAPS/TexCAPS. Both studies yielded data applicable to the consideration of nonprescription status for lovastatin 20 mg.

Both EXCEL and AFCAPS showed agreement in their respective results for the lipid profile effects of lovastatin 20 mg. Both studies confirmed that after 12 to 18 weeks of therapy, users of lovastatin 20 mg are likely to achieve reductions of 17, 24, and 6% in TC, LDL-C, and triglycerides, respectively and a 7% increase in HDL-C. Furthermore, although not primarily designed to assess efficacy, the CUSTOM Actual Use study also demonstrated similar changes to participants' lipid profiles with lovastatin 20 mg, although a change in HDL-C was not observed in this uncontrolled study.

AFCAPS/TexCAPS evaluated the efficacy of lovastatin (20 and 40 mg) with respect to CHD outcomes. Because AFCAPS/TexCAPS participants were predominantly at intermediate risk (75% of participants), this very large, long-term, placebo-controlled trial is uniquely suited for use in helping to define the benefit of lovastatin among the OTC-statin eligible population. The OTC statin-eligible population, by definition, is an intermediate risk population that has multiple CHD risk factors (2 or more) and a calculated CHD risk $\leq$ 20%[23]. AFCAPS/TexCAPS demonstrated a 37% reduction in the primary end point of acute major coronary events (defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) with lovastatin versus placebo. Similar degrees of reduction were also seen for the secondary endpoints of revascularization (33%), fatal and nonfatal myocardial infarction (40%), fatal and nonfatal cardiovascular events (25%), and fatal and nonfatal coronary events (25%). AFCAPS/TexCAPS has substantial generalizability to the OTC-statin eligible population now being considered for nonprescription lovastatin 20 mg.

With nonprescription availability of lovastatin 20 mg, some lower risk individuals are likely to use the drug despite the proposed non-prescription label, yet still could attain benefit. The AFCAPS/TexCAPS population had about a 6% 10-year risk for CHD. Although most of the population treated with lovastatin in AFCAPS/TexCAPS is consistent with the ATP III guidelines for therapy with statins, around 35% of the participants treated with lovastatin are not currently recommended for such therapy. This large cohort from AFCAPS/TexCAPS was at lower CHD risk than the remainder of the AFCAPS/TexCAPS population yet still benefited (with a 34% relative risk reduction in CHD events) from therapy with lovastatin.

4. Estimation of CHD Risk Reduction in the OTC Population

Because AFCAPS/TexCAPS demonstrates a substantial degree of external validity to the non-prescription lovastatin treatment-eligible population, it was important to further clarify the effect of lovastatin 20 mg on this subpopulation from AFCAPS/TexCAPS. Three specific subpopulations from AFCAPS/TexCAPS were analyzed for efficacy with lovastatin 20 mg: MEVACOR™ OTC-eligible Participants, MEVACOR™ OTC eligible participants who remained on 20 mg (non-titrators), and the MEVACOR™ OTC label-eligible participants achieving the MEVACOR™ OTC label-target goal (<130 mg/dL). These 3 subpopulations treated with lovastatin were compared with similarly matched participants on placebo. As shown by Table C-8 and Figure C-4 there were highly significant reductions (compared with the appropriate placebo-matched subpopulations) in the primary endpoint for all 3 subpopulations that ranged from 45% to 53%. These reductions in the primary endpoint using lovastatin 20 mg calculated by post hoc analysis are consistent with the 37% reduction of the primary endpoint for all AFCAPS/TexCAPS participants with lovastatin 20 and 40 mg. Therefore, it is reasonable to conclude that the efficacy of lovastatin 20 mg is consistent with the overall efficacy demonstrated for lovastatin in AFCAPS and likely to be similar to that seen among MEVACOR™ OTC label-eligible consumers taking non-prescription lovastatin 20 mg.

The post hoc analysis for lovastatin 20 mg in the AFCAPS/TexCAPS population demonstrates a clinically significant reduction in the primary endpoint for all 3 subpopulations analyzed. Furthermore, the number needed to treat (NNT) to avoid a CHD event over the chosen 72-month (6 year) time period for Kaplan-Meier event rates is similar for these subpopulations (ranging from 25-28) and compares favorably with the overall NNT (34) from the lovastatin-treated population in AFCAPS/TexCAPS. These values must be interpreted with caution due to limitations of the post hoc subset analysis and lack of randomized placebo group. However, collectively, these analyses support the efficacy of lovastatin 20 mg in the primary prevention of CHD events in the proposed MEVACOR™ OTC label-eligible population.

The real risk reduction will vary dependent upon a number of factors, including the actual CHD risk profile of the individual and the OTC population in general. It should be noted that the population that purchased and used the product in the CUSTOM study had a wide range of baseline CHD risk (See Section G.3.3.1).

5. Efficacy and Benefit Conclusions

In summary, the lipid lowering efficacy of lovastatin 20 mg has been demonstrated in two large, long-term, randomized controlled clinical trials. Based on data from these studies, beneficial lipid modifying effects are to be expected in OTC eligible populations that can lead to an effective reduction in overall CHD risk for those consumers that use the product appropriately over the long term. Lovastatin 20 mg is therefore an appropriate dose for the proposed MEVACOR™ OTC label-eligible population, based on its demonstrated efficacy in this CHD risk group. When this dose was tested under actual use conditions, the expected average reduction in LDL-C was observed and a substantial reduction in CHD risk can be achieved if used appropriately over the long-term.

D. PHARMACOKINETICS AND DRUG METABOLISM

1. Background

The 20-mg tablet of lovastatin proposed for the nonprescription market is the same composition and is made by the same process as the prescription formulation except for debossing in order to give it a unique image.

Lovastatin is a lactone-pro-drug which, upon hydrolysis to the β-hydroxyacid (L-154819), is a potent inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the primary step in the cholesterol synthetic pathway in the liver, the conversion of HMG-CoA to mevalonic acid.

Following oral administration, the drug is incompletely absorbed from the gastrointestinal tract, undergoes first-pass extraction in the liver, its primary site of action, and is extensively metabolized to both active and inactive metabolites. The parent lactone form is converted to the active β-hydroxyacid (L-154819) by esterases and by nonenzymatic hydrolysis. In addition to L-154819, 3 other downstream metabolites with HMG-CoA reductase inhibitory activity are detectable in the systemic circulation of man. Additionally, lovastatin and other lactones are present in plasma. These are not inhibitors of the enzyme but are detected following base hydrolysis to convert lactones to their corresponding β-hydroxyacids (see Figure D-1). Given that several of these metabolites are active HMG-CoA reductase inhibitors, it is critical that drug equivalents (as β-hydroxyacids) are quantified in the general circulation since myopathy associated with these cholesterol-lowering agents may be associated with excessive inhibition of cholesterol synthesis in skeletal muscle. Measurement of drug equivalents (as β-hydroxyacids) may be accomplished with use of an enzyme inhibition assay which has as its basis the inhibition of HGM-CoA reductase.

In addition, an LC/MS/MS analytical method has been recently developed to measure lovastatin and its active hydroxyacid metabolite in plasma and this assay was used to assay plasma samples from a multiple-dose study which compared 10- and 40-mg doses of lovastatin, and an interaction study with lovastatin 40-mg and grapefruit juice.

An overall summary of the plasma profile parameters for lovastatin-derived HMG-CoA reductase inhibitory activity from 5 definitive studies for lovastatin is presented in Table D-1.

Figure D-1

Lovastatin Metabolism

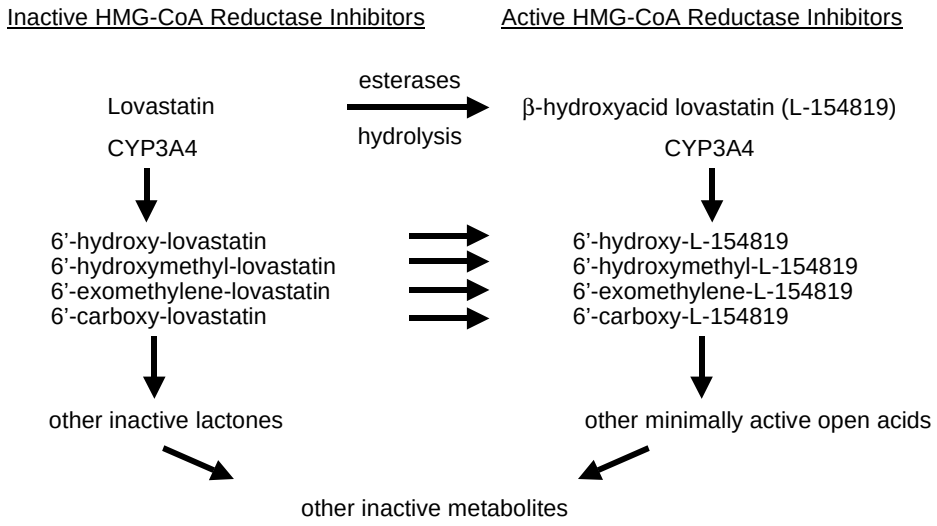


Table D-1

Overall Summary of Plasma Profile Parameters for Lovastatin-Derived HMG-CoA Reductase Inhibitory Activity
(Mean ± SD)

Study/Dosage Form	C_{max} (ng eq/mL)		T_{max} (h)		AUC_{24} (ng eq•hr/mL)		$F^{\dagger}_{rel}$	
	Active	Total	Active	Total	Active	Total	Active	Total
Dose–Proportionality/Food N=12								
3 x 20-mg CT	24.6±24.5	38.8±31.4	4.1±2.2	3.3±2.4	135±118	263±126	--	--
3 x 30-mg CT	26.4±24.8	47.4±31.2	3.0±1.1	3.2±1.8	227±231	425±299	1.04	1.00
3 x 40-mg CT	39.4±37.1	62.1±42.9	3.5±1.9	3.2±2.5	291±279	512±311	1.14	0.91
3 x 20-mg CT (w/food)	46.7±31.0	91.5±37.6	2.6±1.0	2.3±0.9	233±180	392±230	1.54	1.38
Multiple-Dose Kinetics, N=10								
4 x 20-mg CT—single dose	17.6±15.0	54.8±42.6	2.4±1.0	2.0±1.4	126±81.3	409±199		
4 x 20-mg CT—7^{th} dose	26.2±17.7	71.5±37.7	2.2±0.8	2.0±1.0	216±161	584±279		
Propranolol Interaction, N=12								
80-mg DFC	15.9±9.6	40.9±17.8	5.0±6.1	4.9±6.3	61.3±41.3	167±85.1		
Grapefruit Juice Interaction, N=15								
40-mg CT with water	22.0±9.0	40.2±21.4	3.8±1.8	3.5±1.9	139.9±46.1	227.7±64.6		
Low-Dose Multiple-Dose, N=14								
10-mg CT Day 1	4.9±1.9	12.0±4.4	4.8±2.1	3.6±2.2	30.5±13.3	63.3±20.5		
10-mg CT Day 10	5.2±1.7	14.1±4.1	3.5±2.0	2.5±1.2	29.6±10.5	67.4±14.9		
40-mg CT Day 1	26.2±8.9	50.5±15.0	5.1±2.4	4.3±2.2	156±60.7	276±85.7		
40-mg CT Day 10	22.1±7.2	48.7±22.5	5.4±3.2	4.3±3.1	160±68.5	297±106		

†Frel=Relative Bioavailability, geometric mean.

2. In Vivo Analytical Methods

Three analytical methods have been used to quantify lovastatin, its active β-hydroxyacid metabolite L-154819, or the inhibitors of HMG-CoA reductase resulting from the administration of lovastatin. The first method quantifies lovastatin and L-154819, by high-performance liquid chromatography [HPLC] with UV detection. The second method also quantifies lovastatin and L-154819 by liquid chromatography with tandem mass spectrometric detection (LC/MS/MS). The third method quantifies the sum of L-154819 and other inhibitors in plasma (weighted by their respective inhibitory binding constants) by assessing the inhibition of HMG-CoA reductase activity [69]. Base hydrolysis of the plasma samples permits an assessment of latent inhibitors such as lovastatin and other lactone metabolites.

3. In Vitro and Nonclinical Data

The disposition of lovastatin has been studied in various animal species. Approximately 30% of an orally administered dose of lovastatin is absorbed in the mouse, rat, and dog. All species convert lovastatin to its β-hydroxyacid form, L-154819, as shown by its presence in their respective biological fluids. The reverse has also been shown in the rat and dog in that lovastatin can be found in biological fluids following the administration of L-154819. Lovastatin is hydrolyzed substantially faster in rodent plasma compared to dog or human plasma.

The formation of polar metabolites is much more extensive in rodents compared to the dog. This more extensive metabolism is reflected in a substantially smaller fraction of lovastatin and L-154819 being recovered in the bile of the rat and mouse compared to the dog. In addition, a taurine conjugate of L-154819 is found in rodents and not in the dog. It appears that oxidative pathways are relatively more important in rodents compared to the dog.

A metabolite, 6'-hydroxy-L-154819, which is approximately 70% as potent as L-154819, appears to be formed in all species studied, including man. In addition, another inhibitor has been found in the dog and rat and identified as the 6'-exomethylene metabolite [69]. These inhibitors are also present in human plasma or bile. Thus, dog and man are similar in that both seem to have the same inhibitory metabolites present in plasma or bile. Fewer inhibitors and less inhibitory activity, relative to inactive metabolites, are present in mouse plasma relative to dog plasma. More recent studies have documented that lovastatin and L-154819 metabolism is catalyzed by cytochrome P-450 (CYP) 3A with no involvement of CYP2A1, CYP2C11, CYP2E1, CYP2B1/2, CYP1A1, or CYP1A2 [70; 71].

The inhibition of CYP3A4 activity (as measured by testosterone 6β-hydroxylation) by lovastatin was studied in an in vitro human liver microsomal system. The in vitro inhibition constant (K_i = 7.7 μM) is much higher than the clinically achievable plasma concentrations and, in particular, higher than the maximal plasma concentrations (C_{max}) of total HMG-CoA reductase inhibitory activity (~0.25 μM) for lovastatin at its maximum approved prescription dose (80 mg). Thus, lovastatin at the proposed OTC dose would not inhibit the metabolism of other CYP3A4 substrates.

4. Human Pharmacokinetics of Lovastatin

4.1 Single Oral Dose Pharmacokinetics

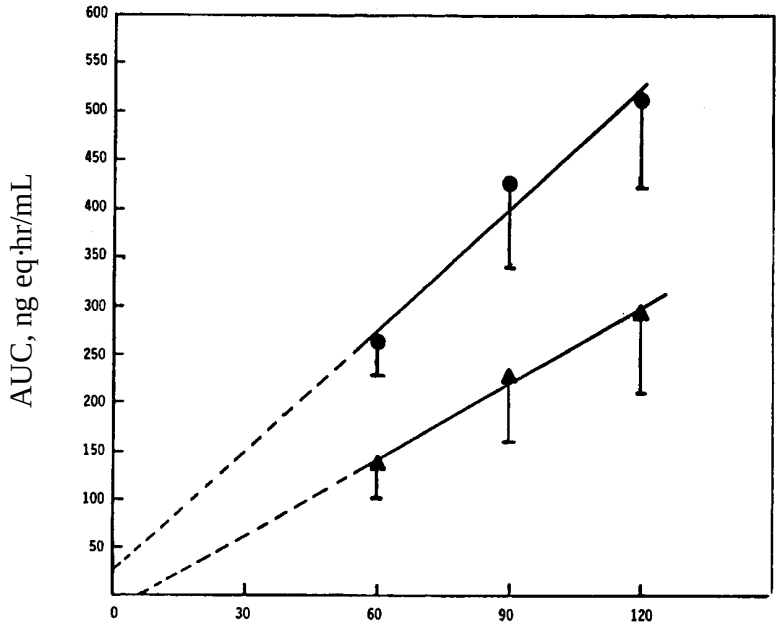
Following single oral doses of 60, 90, and 120 mg of lovastatin administered to 12 healthy male volunteers, the plasma profile parameters for HMG-CoA reductase inhibitors indicate that the pharmacokinetics of lovastatin are linear over the 60- to 120-mg dose range. A plot of the observed mean inhibitor AUC values versus dose (Figure D-2) also shows that the regression intercepts are close to zero, suggesting that linear kinetics prevail over the therapeutic dosage range.

4.2 Multiple Oral Dose Pharmacokinetics

Once daily doses of lovastatin 80 mg were administered to 10 patients with primary hypercholesterolemia and the data indicated that steady state was obtained within 2 to 3 days. Mean AUC values for active and total inhibitors exhibited modest accumulation increasing by ~50% by the time steady state was attained.

Figure D-2

Dose Versus Mean (SEM N=12) AUC24 of Active (▲) and Total (●)
Inhibitor Concentrations in Human Plasma Following Single Oral Doses of Lovastatin
Administered as 3 x 20-, 3 x 30-, or 3 x 40-mg Tablets



The proposed nonprescription lovastatin dose is 20 mg taken once daily with the evening meal. The lowest prescription dose in the original marketing application is 10 mg but no pharmacokinetic studies were conducted at that dose since the technical capabilities of analytical methods were insufficient to detect plasma concentrations of inhibitory activity. Recent enhancements in analytical technology for the enzyme inhibition assay and for the newly developed LC/MS/MS assay now make such studies feasible with dosages as low as 10 mg. Hence, a study was undertaken in healthy subjects (N=14) to investigate the multiple-dose pharmacokinetics of lovastatin, L-154819, and HMG-CoA reductase inhibitory activity following once-daily (x 10 days) evening doses of lovastatin 10 and 40 mg.

Plasma concentrations (AUC) of active or total HMG-CoA reductase inhibitory activity increased in approximately a linear fashion for the 10- and 40-mg doses of lovastatin administered in this study. Also there was very little accumulation (<10% of AUC) of inhibitory activity across the 10 days of dosing. The same was true for lovastatin and L-154819. Plasma concentrations of either chemical entity increased nearly in proportion to the dose of lovastatin administered and there was little, if any, accumulation over the 10 days of dosing.

Taken together with the data presented earlier for 60-, 90-, and 120-mg doses of lovastatin, these data indicate that the disposition of lovastatin is independent of dose across a 10- to 120-mg dose range as was inferred from the earlier data alone. This allows one to predict with confidence the effects of drug interactions, organ failure, and possibly other events on the plasma profiles of inhibitory activity following administration of lovastatin once a baseline has been established.

4.3 Effect of Renal Impairment

Six hypercholesterolemic patients with severe renal impairment (GFR=10 to 30 mL/min) and 7 healthy control subjects received a single oral 80-mg dose of ^{14}C-lovastatin (100 μCi) so that the effect of renal impairment on lovastatin disposition would be evaluated. The urinary recovery of radioactivity decreased somewhat in patients with severe renal impairment (~10% vs. ~19% in healthy subjects) and the AUC for active or total inhibitors was 2-fold higher. Although the higher inhibitor levels expected from a 10-mg dose are clearly safe, it is recommended that nonprescription lovastatin should not be used in patients with renal insufficiency without consultation with a physician.

4.4 Effect of Age and Gender

The effects of age and gender on plasma HMG-CoA reductase inhibitory activity following multiple doses of lovastatin (80 mg) were investigated in 16 elderly (7 males and 9 females) and 18 young (9 males and 9 females) hypercholesterolemic patients [72]. Elderly subjects ranged in age from 70 to 79 years while young subjects ranged in age from 19 to 30 years. Following 80-mg doses of lovastatin given daily for 17 days, plasma concentrations of HMG-CoA reductase inhibitory activity were slightly higher (mean AUC 22 to 30% higher) in elderly females than in elderly males. The same was true for young females versus young males where mean AUC was 35 to 48% higher. These differences were not significant. Mean AUC for inhibitors was also higher (33 to 56%) in elderly versus young patients, but the only comparison reaching significance was that for total inhibitors in elderly versus young males. None of these differences indicated that dosage adjustments were necessary for elderly versus young patients or for female versus male patients.

5. Pharmacokinetic Drug Interactions

5.1 Effect of Food

Twelve healthy volunteers received a 60-mg dose of lovastatin while fasting and immediately following a standard test meal which was similar in fat content to the expected diet of patients being treated for hypercholesterolemia. In the nonfasting state, peak plasma concentrations of both active and total inhibitors occurred sooner and were higher than in the fasting state. On average, AUC values following the test meal were about 50% higher than those achieved under fasting conditions. It is recommended in product labeling that lovastatin be given with meals as in clinical studies of efficacy.

5.2 Effect of Grapefruit Juice and Other CYP3A4 Inhibitors

Grapefruit Juice

Grapefruit juice has been shown to be an inhibitor of CYP3A4 and lovastatin is a substrate for CYP3A4. To investigate the effect of grapefruit juice on lovastatin, L-154819, and lovastatin-derived HMG-CoA reductase inhibitory activity profiles, sixteen healthy male subjects consumed 8 ounces of regular-strength grapefruit juice (12 ounces of concentrate diluted with 3 x 12 ounces of water) or water daily with breakfast for 4 days (juice with breakfast is common). In the evening of Day 3, each subject received a single 40-mg dose of lovastatin (it is recommended that lovastatin be taken after the evening meal). Midazolam, a sensitive probe for CYP3A4 inhibition, was included as a positive control in this study and subjects received a 2-mg oral solution dose of midazolam (prepared from commercially available VERSED™, Roche Laboratories [intravenous formulation]), 1 hour after the morning glass of grapefruit juice or water on Day 3.

Midazolam results exhibited the anticipated inhibition of CYP3A4-mediated metabolism by grapefruit juice as the mean plasma AUC for midazolam increased by 2.4-fold. On the other hand, grapefruit juice had a minimal effect on plasma profiles of lovastatin-derived HMG-CoA reductase inhibitory activity. Mean AUC and C_{max} for either active or total inhibitory activity increased by 30 to 42% in the presence of grapefruit juice. The effect of grapefruit juice on the pharmacokinetics of lovastatin and L-154819 was somewhat greater, but still relatively small. The mean AUC and C_{max} for lovastatin approximately doubled (94 to 128%) under the influence of grapefruit juice, a 3-fold greater increase than was noted for the range of metabolites with actual HMG-CoA reductase inhibitory activity. The plasma $t_{1/2}$ of lovastatin was not affected. The effect of grapefruit juice on L-154819 was less as mean AUC and C_{max} increased by 57% and 65%, respectively. These effects are small when compared to increases in lovastatin and L-154819 AUC (12 to 15 fold and 4 to 5 fold, respectively) reported when lovastatin was given with much higher amounts of grapefruit juice (200 mL of double-strength grapefruit juice (12 ounces of concentrate diluted with 12 ounces of water) 3 times daily for 2 days followed by 200 mL of double-strength grapefruit juice given with, and 0.5 and 1.5 hours after, an 80-mg morning dose of lovastatin) [73]. Unfortunately, the effect on HMG-CoA reductase inhibitors was not measured in that grapefruit juice study.

Other CYP3A4 Inhibitors

Several clinical drug-interaction pharmacokinetic studies assessing the effect of CYP3A4 inhibitors on lovastatin kinetics have been published since the original marketing application. However, most have only examined parent lovastatin rather than total inhibitors. Itraconazole increased lovastatin AUC 19-fold [74]. Oral erythromycin (500 mg P.O. (by mouth) 3 times daily for 7 days) was shown to increase the plasma AUC and C_{max} of lovastatin by 5.7-fold and 5.3-fold, respectively, following multiple oral dosing with lovastatin (40 mg P.O. once daily for 7 days) in healthy subjects [75]. In kidney transplant patients, cyclosporine (2 to 6 mg/kg/day) led to a 20-fold elevation (versus historical values) in the plasma AUC of lovastatin (GC-MS) after multiple oral dosing with lovastatin (20 mg P.O. once daily for 28 days) [76]. Diltiazem administration (120 mg SR P.O. twice daily for 2 weeks) resulted in a 3.6-fold and 4.3-fold increase in the plasma AUC and C_{max} of lovastatin, respectively, following a single oral dose of lovastatin 20 mg in healthy subjects [77]. Isradipine after multiple doses (5 mg P.O. twice daily for 5 days) had no significant effect on plasma concentrations of lovastatin or total HMG-CoA reductase inhibitors following multiple doses of lovastatin (20 mg P.O. once daily for 5 days) in healthy subjects [78].

The grapefruit juice study conducted by Merck showed that the magnitude of pharmacokinetic effect of a CYP3A4 inhibitor on the plasma AUC of lovastatin (by chemical assay) is at least 3 times greater than that on the plasma AUC of active/total HMG-CoA reductase inhibitory activity (by enzymatic assay). The enzymatic assay results are more clinically relevant since the rare myopathies associated with HMG-CoA reductase inhibitors and other cholesterol-lowering drugs are believed to be the result of excessive inhibition of cholesterol synthesis in skeletal muscle and it is likely that all of the circulating active inhibitors of HMG-CoA reductase might cause or contribute to myopathy. Even so, in the presence of one of the more potent inhibitors of the CYP3A4 pathway such as itraconazole, the systemic exposure to HMG-CoA reductase inhibitory activity in a patient on the 20-mg dose of lovastatin would be expected to exceed the plasma exposure observed following 80-mg of lovastatin, the maximum approved prescription dose. Thus, proposed labeling for nonprescription lovastatin warns against taking lovastatin with drugs that are strong inhibitors of CYP3A4.

Summary

Daily morning consumption of regular-strength grapefruit juice with breakfast has a minimal effect on plasma concentrations of HMG-CoA reductase inhibitory activity (<50% increase in AUC or C_{max}) following a 40-mg evening dose of lovastatin. The effects on lovastatin and L-154819 plasma concentrations are somewhat greater (<2.3-fold increase in AUC or C_{max}), but small by comparison to effects noted with other more potent CYP3A4 inhibitors or unrealistic consumption of grapefruit juice. Based on its minimal effect on plasma concentrations of HMG-CoA reductase inhibitors following evening oral administration of lovastatin, daily consumption of moderate amounts of regular-strength grapefruit juice does not require adjustment of the lovastatin dose.

In conclusion, the effects of other more potent CYP3A4 inhibitors on plasma concentrations of lovastatin derived HMG-CoA reductase inhibitory activity are greater than the effect of grapefruit juice. The clinical significance of this interaction at doses in the 20 to 40 mg range appears to be minimal (See Section E. Safety, 4.4 Drug-Drug Interaction). Nonetheless, the use of nonprescription lovastatin together with strong inhibitors of CYP3A4 is not recommended (itraconazole, ketoconazole, erythromycin, clarithromycin, nefazodone, cyclosporine, HIV protease inhibitors and grapefruit juice >1 quart/day).

6. Human Pharmacology Conclusions

- Lovastatin is an inactive lactone which, upon hydrolysis, is converted to the β-hydroxyacid, L-154819, which is an inhibitor of HMG-CoA reductase.
- Lovastatin and its β-hydroxyacid (L-154819) are highly bound (>95%) to human plasma proteins.
- Lovastatin is extensively metabolized to active and inactive metabolites including, L-154819, and 4 other lactone: β-hydroxyacid pairs, all of which account for ~80% of the total HMG-CoA reductase inhibitory activity observed in plasma.
- Lovastatin at the 20-mg dose is not an inhibitor of CYP3A4 (K_i = 7.7 μM) in humans.
- Biliary excretion is an important route of elimination for drug from the body.
- L-154819 is rapidly cleared from the body (total body clearance and $t_{½}$ averaged 639 mL/min and 1.5 hours, respectively).
- The systemic availability of L-154819 following an oral dose of lovastatin is less than 9% of the dose because of first-pass hepatic extraction.
- The plasma AUC of active and total HMG-CoA reductase activity is increased 2-fold in patients with severe renal impairment (GFR=10 to 30 mL/min). Nonprescription lovastatin should not be used in patients with renal insufficiency without consultation with a physician.
- When lovastatin is administered with food, as in clinical studies, the AUCs of active and total inhibitors are about 50% higher compared to administration in the fasting state. For maximum benefit, lovastatin, including nonprescription lovastatin, should be given with meals.
- With lovastatin dosages of 10-, 40-, 60-, 90-, and 120-mg, peak concentrations are achieved in 3 to 5 hours and the AUC and C_{max} of both active and total HMG-CoA reductase inhibitory activity in plasma increase nearly proportionally with dose. With once-a-day dosage regimens of lovastatin (10-, 40-, or 80-mg) there is modest steady-state accumulation of active and total inhibitors in plasma (<10 to 50%). These data indicate that the pharmacokinetics of lovastatin are, in general, linear throughout the therapeutic dosage range.

- The use of nonprescription lovastatin together with strong inhibitors of CYP3A4 is not recommended (itraconazole, ketoconazole, erythromycin, clarithromycin, nefazodone, cylclosporine, HIV protease inhibitors, and grapefruit juice >1 quart/day).
- No dose adjustment is required during coadministration of nonprescription lovastatin with less potent inhibitors of CYP3A4, including daily consumption of regular-strength grapefruit juice (up to 8 ounces).
- The proposed labeling should reduce the likelihood that strong CYP3A4 inhibitors will be used concomitantly with nonprescription lovastatin.

E. SAFETY OF LOVASTATIN

1. Introduction

This Safety Summary provides a comprehensive review of the extensive data available with prescription MEVACOR™ (lovastatin 10 to 80 mg) as well as the safety data from the Nonprescription Lovastatin Clinical Program. Lovastatin (MEVACOR™) has been marketed since 1987 as a prescription drug for the reduction of elevated cholesterol levels and is currently approved and marketed in ~65 countries worldwide, including the United States. According to data from IMS Health, over 100 million prescriptions have been written worldwide for lovastatin during the years 1988 to 2003 and over 10 billion tablets have been distributed worldwide. Assuming 1 tablet was taken daily irrespective of dosage strength, there are over 27 million patient-years of treatment experience with lovastatin. The usual recommended starting dose of prescription lovastatin is 20 mg daily and the maximum recommended dose is 80 mg daily. The proposed nonprescription dose of 20 mg daily has been available by prescription and is estimated to account for ~60% of usage (~17,300,000 patient-years of treatment).

A large body of safety information is available from clinical trials and spontaneous reports received during prescribed use of lovastatin 10 to 80 mg per day. These data clearly establish the safety of doses at and above the dose that is proposed for nonprescription use.

The most comprehensive and informative data come from 2 large, placebo-controlled, published postmarketing trials of lovastatin: The Expanded Clinical Evaluation of Lovastatin [EXCEL (N=8,245)] studied doses of 20 to 80 mg/day, and the Air Force, Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS (N=6,605)] studied 20 to 40 mg/day. Together, these studies evaluated almost 15,000 participants over prolonged periods of treatment in a rigorous and placebo-controlled fashion. They provide strong evidence that lovastatin at doses of 20 mg and greater is generally well tolerated by a diverse patient population. The type and frequency of adverse experiences with lovastatin 20 mg was generally similar to placebo. This experience provides compelling evidence that the 20-mg dose of lovastatin is generally well tolerated.

Merck maintains a database of all adverse experiences spontaneously reported to the company during marketed use of its products. This Worldwide Adverse Experience System (WAES) offers the opportunity to monitor adverse experiences that have occurred during the very extensive marketed use of prescription lovastatin since 1987. Spontaneous reports are those for which the reporting source is either a health care provider, a patient (consumer), a report in the literature, or a governmental agency. This is a voluntary system and therefore data are often incomplete. However, the ability to monitor, even in a limited way, the large, uncontrolled population that has been exposed to lovastatin is a valuable tool to detect infrequent and previously unrecognized adverse experiences associated with the drug. Whenever one carries out or reviews an analysis of

spontaneous report data, one should bear in mind that many factors, other than the actual incidence rates, may influence the reporting rates of different AEs, for different drugs, in patients with different possible risk factors. Variables such as severity and novelty of the event, different countries, perceived relationship to the drug, adverse effects of related drugs, physician awareness, publicity and time since launch may all affect reporting rates.

Review of these data confirms that lovastatin is generally well tolerated under prescription use conditions in wider populations and without the closer monitoring commonly associated with clinical trials. A comprehensive review of the WAES data for this submission did not reveal any previously unrecognized adverse experiences of potential concern associated with lovastatin.

Based on the prescription labeling and clinical experience, there are 3 primary safety issues that must be addressed when considering suitability for nonprescription use of lovastatin 20 mg: the risk of hepatotoxicity, the risk of myopathy, and the risk with inadvertent use during pregnancy. This Safety Summary reviews each of these issues and concludes that the risks are very low and can be managed with appropriate warnings in the label, together with the overall MEVACOR™ OTC Self-Management System, which provides overall education and regular reinforcement of the key safety messages when using MEVACOR™ OTC.

2. Safety Profile—EXCEL and AFCAPS/TexCAPS

2.1 EXCEL

EXCEL was a randomized, double-blind, parallel, 48-week study. Lovastatin was compared with placebo in 8245 patients with hypercholesterolemia (TC 240 to 300 mg/dL and LDL-C >160 mg/dL). Patients with hypercholesterolemia were randomized into 5 similar groups (approximately 1650 per group) taking 1 of 4 dosage regimens of lovastatin (20 and 40 mg once daily, 20 and 40 mg twice daily), or placebo [13]. There was no dose titration during the study.

Clinical adverse experiences reported as possibly, probably, or definitely drug related occurring in ≥1.0% in any one treatment group are presented in Table E-1. The percentage of patients with serious clinical adverse experiences by body system are listed in Table E-2. The safety profile of the lovastatin doses and placebo were generally comparable. None of the adverse experiences in Tables E-1 and E-2 demonstrated a statistically significant increase in incidence with lovastatin treatment. EXCEL demonstrates a clear margin of safety for the proposed OTC dose of lovastatin. Doses up to 4 times the proposed OTC dose were well tolerated when taken for approximately 1 year.

Table E-1

Percent of Patients With Specific Drug-Related† Clinical Adverse Experiences by Body System With an Incidence ≥1% in Any One Treatment Group EXCEL (48 Weeks)

	Placebo (N=1663)	Lovastatin 20 mg every evening (N=1642)	Lovastatin 40 mg every evening (N=1645)	Lovastatin 20 mg twice daily (N=1646)	Lovastatin 40 mg twice daily (N=1649)
	%	%	%	%	%
Number of patients with any drug-related adverse experiences	374 (22.5)	399 (24.3)	401 (24.4)	399 (24.2)	421 (25.5)
Number of patients without any drug-related adverse experience	1289 (77.5)	1243 (75.7)	1244 (75.6)	1247 (75.8)	1228 (74.5)
Body as a Whole/Site Unspecified					
Asthenia	1.4	1.7	1.4	1.5	1.2
Digestive System					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal System					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System and Psychiatric Disorders					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin and Skin Appendage					
Rash	0.7	0.8	1.0	1.2	1.3
Special Sense Disorders					
Blurred vision	0.8	1.1	0.9	0.9	1.2

† Determined by the investigator to be possibly, probably or definitely drug related.
Although a patient may have had two or more drug-related adverse experiences, the patient is represented only once in the body system total.

Table E-2

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
EXCEL (48 Weeks)

	Placebo N=1663	Lovastatin 20 mg every evening N=1642	Lovastatin 40 mg every evening N=1645	Lovastatin 20 mg twice daily N=1646	Lovastatin 40 mg twice daily N=1649
	n (%)	n (%)	n (%)	n (%)	n (%)
Number of patients with a serious adverse experience	146 (8.8)	148 (9.0)	132 (8.0)	137 (8.3)	166 (10.1)
Number of patients without a serious adverse experience	1517 (91.2)	1494 (91.0)	1513 (92.0)	1509 (91.7)	1483 (89.9)
Body as a whole/site unspecified	27 (1.6)	23 (1.4)	29 (1.8)	30 (1.8)	37 (2.2)
Cardiovascular System	73 (4.4)	73 (4.4)	59 (3.6)	63 (3.8)	72 (4.4)
Digestive System	17 (1.0)	18 (1.1)	19 (1.2)	18 (1.1)	18 (1.1)
Endocrine System	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
Hematologic and Lymphatic System	4 (0.2)	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)
Metabolic, Nutritional and Immune System	0 (0.0)	1 (0.1)	3 (0.2)	2 (0.1)	1 (0.1)
Musculoskeletal System	17 (1.0)	12 (0.7)	8 (0.5)	19 (1.2)	16 (1.0)
Nervous System and Psychiatric Disorders	7 (0.4)	9 (0.5)	8 (0.5)	8 (0.5)	14 (0.8)
Respiratory System	8 (0.5)	8 (0.5)	7 (0.4)	10 (0.6)	12 (0.7)
Skin and Skin Appendage	6 (0.4)	11 (0.7)	5 (0.3)	3 (0.2)	12 (0.7)
Special Sense Disorders	9 (0.5)	7 (0.4)	5 (0.3)	3 (0.2)	3 (0.2)
Urogenital System	14 (0.8)	18 (1.1)	24 (1.5)	21 (1.3)	26 (1.6)

Although a patient may have had two or more serious adverse experiences, the patient is counted only once in the body system total.

2.2 AFCAPS/TexCAPS

AFCAPS/TexCAPS was a randomized, double-blind, placebo-controlled study. The purpose was to evaluate lovastatin versus placebo in primary prevention of CHD in 6605 participants over a median duration of 5 years. The participants were predominately healthy men and women with average total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C), below average high-density lipoprotein (HDL) cholesterol, and at least one CHD risk factor, namely age, ≥45 years for men and ≥55 years for women. The dose of lovastatin was initiated at 20 mg/day. The dose was increased to 40 mg daily at Week 18 if the patient's LDL-C level was >110 mg/dL.

The profile of serious adverse experiences by body system is shown in Table E-3. Adverse experiences are included irrespective of drug relationship. Participants are only counted once per category. The incidence of serious adverse experiences between treatment groups was compared using Fisher's exact test. The total number of participants experiencing any serious adverse experience was 1131 (34.2%) in the lovastatin group and 1126 (34.1%) in the placebo group (p=0.938). The cumulative incidence of serious adverse experiences in AFCAPS/TexCAPS was greater than in EXCEL, as would be expected given the 5 years of treatment.

As expected from the efficacy results, there were significantly fewer serious cardiovascular adverse experiences in the lovastatin group than the placebo group (260 versus 310; p=0.028). In the Nervous System and Psychiatric Disorders body system there were significantly more serious adverse experiences in those receiving lovastatin compared with placebo (62 versus 38; p=0.020); however, a treatment-group comparison of the types of disorders revealed no significant differences. The most frequently reported serious adverse experiences of the nervous system were falling (9 on lovastatin versus 7 on placebo), radiculopathy, lumbar (6 versus 4), and radiculopathy, cervical (4 versus 5). Fewer than 4 participants per treatment group experienced other types of serious adverse experiences of the nervous system.

Table E-3

Number (%) of Participants With Specific Serious Clinical Adverse Experiences by Body System—AFCAPS/TexCAPS (Average 5 Years Follow-Up)

	Lovastatin (20-40 mg (N=3304)	Placebo (N=3301)	Between-Group
	N (%)	n (%)	p-Value
Participants with any serious adverse experiences	1131 (34.2)	1126 (34.1)	0.938
Body as a Whole/Site Unspecified	169 (5.1)	179 (5.4)	0.582
Cardiovascular System	260 (7.9)	310 (9.4)	0.028
Digestive System	163 (4.9)	173 (5.2)	0.576
Endocrine System	82 (2.5)	88 (2.7)	0.642
Musculoskeletal System	153 (4.6)	147 (4.5)	0.768
Nervous System and Psychiatric Disorders	62 (1.9)	38 (1.2)	0.020
Respiratory System	85 (2.6)	89 (2.7)	0.759
Skin and Skin Appendage	265 (8.0)	243 (7.4)	0.332
Urogenital System	243 (7.4)	256 (7.8)	0.545

Nonserious and serious adverse experiences that were determined by the investigator to be drug related were evaluated. There were no significant differences between lovastatin and placebo in the incidence of drug-related adverse experiences. The total number of participants experiencing any drug-related clinical or laboratory adverse experience was 577 (17.5%) in the lovastatin group and 525 (15.9%) in the placebo group (p=0.092).

Long-term, chronic use of lovastatin was generally well tolerated. There were no clinically important differences between lovastatin 20 and 40 mg daily and placebo in the number of participants experiencing confirmed clinically important elevations in CK (>10 x Upper Limit of Normal [ULN]) and hepatic transaminases (>3 x ULN). There were no clinically important differences between treatment groups in the incidences of fatal and nonfatal cancers.

2.3 Conclusions From EXCEL and AFCAPS/TexCAPS

Long-term, chronic use of lovastatin was generally well tolerated in both EXCEL and AFCAPS/TexCAPS participants. The safety profile of lovastatin 20 to 40 mg/day was comparable to that of placebo.

3. Spontaneous Reports

This summary presents data summaries and tabulations from spontaneous reports received from the time of MEVACOR™ product launch in September, 1987 through 01-Nov-2003. These safety data reflect over 15 years of clinical experience with lovastatin. Consumer reports are not included in this summary since the lack of a professional diagnosis and detailed follow-up information limits the usefulness of these reports. These spontaneous reports for lovastatin encompass prescription use across all doses.

The number of reports needs to be viewed in the context of the extensive marketed experience with lovastatin (estimated 27,000,000 patient-treatment years). The estimated number of patient-treatment years by total daily dose is: ~1,510,000 for 10 mg (5.5%), 17,280,000 for 20 mg (63%), 7,680,000 for 40 mg (28%), 82,000 for 60 mg (0.3%), and 660,000 for ≥80 mg (2.4%).

Spontaneous reports are divided into serious and nonserious adverse experiences. According to standard regulatory convention, a serious adverse experience is defined as one that: results in death, is life-threatening, results in a persistent or significant disability/incapacity, results in or prolongs hospitalization, is a congenital anomaly, is a cancer, or is the result of an overdose (accidental or intentional). Since April 1, 1998, the definition of a serious adverse experience was expanded to include any report of an "important medical event" (i.e., required medical intervention to prevent one of the aforementioned outcomes).

3.1 Serious Spontaneous Reports by System Organ Class (SOC)

Spontaneous reports are coded using the MedDRA dictionary which is the standard dictionary for regulatory reporting. All spontaneous lovastatin WAES reports were sorted into System Organ Class (SOC) groups and the reporting frequency of adverse experiences within each SOC was calculated by dividing the number of adverse experiences within a category by the total number of reports (N=2,265). Those adverse experiences reported in ≥1% (≥22 reports) of the total spontaneous WAES reports are presented by SOC in Table E-4.

Table E-4

Number of Serious Clinical Adverse Experiences
(≥1% of Total Serious Adverse Experience Reports)
by System Organ Class and Specific Adverse Experience (WAES)

Adverse Experience Term	Lovastatin (2,265 Spontaneous Reports) Number of Reports† and Adverse Experiences‡
Blood and Lymphatic System Disorders	**95**
Cardiac Disorders	**214**
Arrhythmia NOS	23
Cardiac failure congestive	35
Myocardial infarction	39
Eye Disorders	**292**
Cataract, NOS	33
Lens disorder, NOS	188
Gastrointestinal Disorders	**250**
Abdominal pain, NOS	26
Gastrointestinal hemorrhage NOS	25
Nausea	28
Pancreatitis NOS	83
General Disorders and Administration Site	**301**
Asthenia	40
Chest pain	30
Drug interaction NOS	92
Pyrexia	47
Hepatobiliary Disorders	**282**
Cholecystitis NOS	22
Cholelithiasis	27
Hepatic function abnormal NOS	124
Jaundice NOS	25
Immune System Disorders	**25**
Infections and Infestations	**195**
Hepatitis NOS	104
Pneumonia NOS	26
Injury, Poisoning, and Procedural	**50**
Overdose, NOS	29

Table E-4 (Cont.)

Number of Serious Clinical Adverse Experiences
(≥1% of Total Serious Adverse Experience Reports)
by System Organ Class and Specific Adverse Experience (WAES)

Adverse Experience Term	Lovastatin (2,265 Spontaneous Reports) Number of Reports[†] and Adverse Experiences[‡]
Investigations	**282**
Blood creatine phosphokinase increased	142
Metabolism and Nutrition Disorders	**82**
Musculoskeletal and Connective Tissue Disorders	**677**
Arthralgia	28
Muscle disorder NOS	79
Muscle weakness NOS	64
Myalgia	121
Myositis	92
Rhabdomyolysis	273
Neoplasms Benign, Malignant, and Unspecified (incl. cysts and polyps)	**142**
Nervous System Disorders	**307**
Peripheral neuropathy NOS	34
Psychiatric Disorders	**61**
Renal and Urinary Disorders	**197**
Renal failure acute	49
Renal failure NOS	83
Reproductive System and Breast Disorders	**28**
Respiratory, Thoracic, and Mediastinal	**78**
Dyspnea NOS	25
Skin and Subcutaneous Tissue Disorders	**119**
Rash NOS	26
Vascular Disorders	**133**
Cerebrovascular accident	27

[†] Bold numbers = number of reports within each system organ class.
[‡] Non-bold numbers = number of serious adverse experiences within a system organ class.
Reports with more than one adverse experience are counted in the system organ class pertaining to each adverse experience. Therefore, the sum of adverse experiences may be larger than the total number of reports.
WAES = Worldwide Adverse Experience System; NOS = Not otherwise specified.

A total of 2,265 spontaneous reports classified as serious were received as of 01-Nov-2003 from health care professionals. Six organ classes had more than 274 serious spontaneous reports (approximate reporting rate of ≥1 per 100,000 patient-treatment-years [PTY]): musculoskeletal and connective tissue disorders (677 [2.5 per 100,000 PTY]); nervous system disorders (305 [1.1 per 100,000 PTY]); general disorders and administration site conditions (301 [1.1 per 100,000 PTY]); eye disorders (292 [1.1 per 100,000 PTY]); hepatobiliary disorders (282 [1.0 per 100,000 PTY]); and investigations (282 [1.0 per 100,000 PTY]). These 6 system organ classes are discussed below.

Musculoskeletal and Connective Tissue Disorders

The most frequent serious adverse experiences are rhabdomyolysis (273 reports), myalgia (121 reports) and myositis (92 reports). Some cases of myopathy may have been included in the Investigations SOC (if an elevated creatine phosphokinase was reported). Warnings about the potential for myopathy are included in the prescription circulars for all HMG-CoA reductase inhibitors. See 4.2 of this Safety Section for an in-depth discussion of myopathy.

Nervous System Disorders

The most frequently reported serious adverse experience in this SOC was peripheral neuropathy NOS (34 reports). All other nervous system adverse experiences were reported in fewer than 1% of the serious reports (<22 reports).

General Disorders and Administration Site Conditions

The most frequently reported serious adverse experience in this SOC was drug interaction NOS (92 reports). The potential for drug-drug interactions is discussed in 4.3 of this Safety Section.

Eye Disorders

Within the eye disorders SOC, the most frequently reported serious adverse experiences are cataracts (33 reports) and lens disorders (188 reports), terms generally referring to the same diagnoses. The frequent reporting of these adverse experiences is likely a consequence of the recommendation of slit lamp examination of the lens which appeared as an initial precaution in the product circular when the drug was initially marketed. The recommendation for slit lamp examination of the lens was subsequently removed from the product circular by the FDA in 1991 when evidence demonstrated the absence of clinical adverse effects on the lens.

Hepatobiliary Disorders

Within the hepatobiliary disorders SOC, the most common serious adverse experience was hepatic function abnormal (124 reports). It should be noted that the adverse experience term "hepatitis NOS" is not classified under hepatobiliary disorders, but was the most frequently reported serious adverse experience in the infections and infestations SOC (104 reports). See 4.1 of this Safety Section for an in-depth discussion of elevations of LFTs and other hepatic adverse experiences.

Investigations

Within the investigations SOC, there are 287 reports with serious adverse experiences. The most frequently reported serious adverse experience was blood creatine phosphokinase increased (142 reports). Many of these reports are also counted in the musculoskeletal disorders SOC. Muscle-related safety is further discussed in 4.2 of this Safety Section.

3.2 Spontaneous Reports With Fatal Outcomes

From the launch of lovastatin in September, 1987 to 01-Nov-2003, Merck received 173 spontaneous reports from health care professionals in which a fatal outcome was reported in patients who had been exposed to lovastatin. Given the extensive usage in a patient population with cardiovascular disease, the 173 reports represent a reporting rate of 6.1 deaths per million patient treatment years of lovastatin. As would be expected in a large group of American adults, most of the deaths were due to cardiovascular events or cancer. Deaths due to myopathy or acute liver disease are discussed in 4.2 and 4.1 of this Safety Section.

The reports are divided into categories by primary cause of death, as determined by a Merck physician (Table E-5). If there were multiple causes or diseases, the one that was most likely the primary cause of death is selected for categorization in the table. However, it should be noted that many of these reports described patients with complicated medical histories and it is possible that in some cases multiple factors and/or background conditions contributed to the patient's death. In addition, many reports do not provide complete medical history or follow-up information.

Table E-5

Number of Adverse Experience Reports With Fatal Outcome by Category—
Spontaneous Reports From Healthcare Professionals (WAES)

Category	Total Adverse Experience Reports
Cardiovascular	43
Cancer	27
Muscle	29
Hepatobiliary	17
Fetal death/Abortion	16
Digestive system	4
Nervous system	3
Miscellaneous	34
Total	173
WAES = Worldwide Adverse Experience System.	

Cardiovascular

There are 43 reports of patients who died from cardiovascular adverse experiences while taking or after taking lovastatin. The causes of death included CVA, myocardial infarction, coronary artery disease, congestive heart failure, arrhythmia, cardiac arrest, sudden death, bleeding from a femoral aneurysm, a ruptured aortic aneurysm, unstable angina, and an unknown cardiac disorder. These adverse experiences were often preexisting conditions or a consequence of risk factors cited in the patients' history. They reflect the population chosen for treatment with lovastatin, those with elevated cholesterol and CHD.

As demonstrated in AFCAPS/TexCAPS, patients treated with lovastatin experience a 37% lower incidence of the first major coronary event compared with patients treated with placebo. Based on this result and in view of the use of lovastatin throughout the years, there are no data to suggest a causal role of lovastatin in the exacerbation of a cardiovascular disease.

Cancer

Twenty-seven patients have been reported to have died from cancer while or after taking lovastatin. Types of cancer included hepatobiliary, leukemia/lymphoma, pulmonary, and a miscellaneous group that contained prostate cancer, pancreatic cancer, angiosarcoma, adrenal cancer, metastatic cancer to the liver, primary cancer unknown, and an amelanotic melanoma. There is no pattern of reporting observed for any specific cancer. Considering 27 million patient-treatment years of lovastatin, this is a reporting rate of ~1 cancer per 1 million patient treatment years.

There are significant data from postapproval megatrials to suggest that HMG-CoA reductase inhibitors are not linked to an increased incidence of cancer in humans. In AFCAPS/TexCAPS there was no difference between treatment groups in mortality and incidence of fatal and nonfatal cancer. In 4S, the number of cancers was similar in the simvastatin and placebo group. There was no suggestion of an increase in cancer overall or at any particular site. In view of the absence of predominance of any cancer type reported, the limited numbers of reported cases in WAES, and information from the published literature, there is no evidence lovastatin may induce or promote the development and progression of malignancies.

3.3 Summary of Spontaneous Reports

Recent review of the WAES data does not reveal a new association between lovastatin and an adverse experience not currently included in the prescription labeling. The spontaneous reports generally reflect the known side effects of the drug (myopathy and aminotransferase elevations), previous warnings within the product circular (lenticular disorders), or concomitant disease in the patient population (congestive heart failure, myocardial infarction, pancreatitis, diabetes mellitus).

4. Safety Issues of Special Interest

4.1 Hepatobiliary Adverse Reactions

4.1.1 Introduction

The currently approved U.S. labeling of lovastatin states: "It is recommended that liver function tests be performed before initiation of treatment, at 6 and 12 weeks after initiation of treatment or elevation in dose, and periodically thereafter (e.g., semi-annually)" [79]. This recommendation, which is similar for all drugs in this class [54], is based predominantly on findings from animal toxicology studies and the early clinical studies conducted with lovastatin. Large clinical studies conducted postapproval and spontaneous reports received during marketed use provide reassurance that clinical hepatotoxicity which may be due to lovastatin is exceedingly rare.

The data from this comprehensive review indicate that the risk of significant liver function abnormalities with lovastatin at doses of 20 mg or less is not significantly different than the occurrence observed with placebo. Identifying patients who might need to stop treatment to prevent serious liver injury by routine monitoring of LFTs is an extremely low-yield procedure, particularly at low doses of medication.

HMG-CoA reductase inhibitors may be associated with myopathy accompanied by elevated AST, however ALT is more liver specific, and therefore more relevant.

4.1.2 Postapproval Clinical Studies

EXCEL

In EXCEL no patient in the study experienced hepatitis. Table E-6 displays the number of patients with consecutive elevations >3 x ULN in hepatic transaminases by dose. The incidence rates in the placebo and 20-mg groups were identical. The incidence rates at the 40- and 80-mg doses suggested a dose-dependent effect; however, the incidence at 40 mg was still less than 1%. Additionally, 977 of the 8,245 patients initially randomized continued into the 1-year extension and only 1 patient developed significant increases in ALT or AST.

Table E-6

Number of Patients with Consecutive Elevations >3 x ULN in Hepatic Transaminases During the Initial 48 Weeks of Treatment in EXCEL by Dose

	Lovastatin 20 mg Once Daily	Lovastatin 40 mg Once Daily	Lovastatin 20 mg Twice Daily	Lovastatin 40 mg Twice Daily	Placebo
	(N=1642) n (%)	(N=1645) n (%)	(N=1646) n (%)	(N=1649) n (%)	(N=1663) n (%)
Patients with consecutive elevations in ALT or AST	2 (0.1)	12 (0.9)	11 (0.9)	20 (1.5)	2 (0.1)

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

AFCAPS/TexCAPS

In AFCAPS/TexCAPS, among the 6,605 participants there were no adverse experiences of drug-induced hepatitis that occurred during the study in the lovastatin treatment group. Table E-7 presents the number of participants with one or more, and consecutive elevations greater than 3 x ULN in ALT alone, AST alone, and ALT or AST. The ALT or AST elevations include increases in ALT alone, AST alone, and both ALT and AST. The category of "one or more elevations" includes participants with (1) single, (2) nonconsecutive multiple, and (3) consecutive elevations greater than 3 times ULN. "Consecutive elevations" includes only those participants with at least 2 consecutive elevations greater than 3 x ULN. Elevated hepatic transaminases resulted in the discontinuation of only 6 (0.2%) participants in the lovastatin group and 4 (0.1%) in the placebo group. The 18 lovastatin participants and 11 placebo participants with consecutive elevations shown in Table E-7 are of greater interest than the participants having one or more elevation. The difference in the number of participants between treatment groups experiencing consecutive elevations is very minor demonstrating that lovastatin is not hepatotoxic. The p-value for one or more ALT or AST elevation should be interpreted with caution as the majority of these values were not confirmed with another elevation, the 40-mg dose is included, and there are no multiplicity corrections.

However, it is consistent with the general observation that statin use may be associated with occasional, mild transient elevations [54]. The cause of this is unknown but may be related to cholesterol lowering itself, since these elevations are seen in other classes of lipid-lowering drugs such as ezetimibe [80].

Table E-7

Number of Participants With One or More and Consecutive Elevations >3 Times ULN in Hepatic Transaminases in AFCAPS/TexCAPS

	One or More Elevations			Consecutive Elevations		
	Lovastatin (N=3242) n (%)	Placebo (N=3248) n (%)	p-Value	Lovastatin (N=3242) n (%)	Placebo (N=3248) n (%)	p-Value
ALT	55 (1.70)	38 (1.17)	0.077	17 (0.52)	11 (0.34)	0.263
AST	33 (1.02)	26 (0.80)	0.364	5 (0.15)	4 (0.12)	0.754
ALT or AST	66 (2.04)	44 (1.35)	0.035	18 (0.56)	11 (0.34)	0.199
ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal						

There were 18 participants treated with lovastatin (11/1585 [0.7%] receiving 20 mg and 7/1657 [0.4%] receiving 40 mg) who experienced consecutive transaminase elevations >3 x ULN. For all 18 participants the onset of consecutive elevations was after 12 weeks of treatment. There were no statistical differences between lovastatin 20 and 40 mg and placebo for frequency of consecutive transaminase elevation >3 times the ULN. See Table E-8 for details regarding timing in weeks of the consecutive elevations for both active treatment and placebo groups.

Table E-8

Participants With Successive Elevations in ALT/AST >3 x ULN
Time Interval of Occurrence in AFCAPS/TexCAPS

	Time Interval		
Treatment Group	<6 Weeks	6-12 Weeks	>12 Weeks
Lovastatin (N=18)	0	0	18 (100%)
Placebo (N=11)	0	2 (18%)	9 (82%)
ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.			

Of the 18 lovastatin-treated patients, 14 recovered with continued treatment or had a negative rechallenge with no further significant elevations during the trial. Of the remaining 4 patients, 3 were discontinued and not rechallenged (one patient had a history of hepatitis B and discontinued due to fatty liver; the second patient was discontinued for chronic active hepatitis; and the third patient had baseline LFT elevations and was discontinued due to use of another lipid lowering agent). The fourth patient was discontinued after a positive rechallenge (with increased LFT <2 x ULN) and was diagnosed with cholelithiasis. This fluctuation in LFTs is most likely a result of fluctuations normally seen in patients with chronic liver disease. In support of this, all of these discontinued patients had liver abnormality assessments by the investigator as not related to lovastatin. One patient had elevations before therapy that may have been aggravated by taking lovastatin in combination with another lipid lowering agent.

Additionally, 11 placebo patients had elevation of LFTs >3 x ULN). Four of these patients (36%) were discontinued from the study; one of these 4 patients was discontinued after having a positive rechallenge. Of these 11 placebo participants with successive elevations in ALT or AST >3 x ULN, 10 had normal levels (<1 x ULN) at baseline.

There were 127 participants in the lovastatin group who had ALT elevations between 2 and 3 x ULN. These participants were continued on drug and monitored. In 91 of the 127 participants, subsequent ALT elevations decreased. In 18, the ALT remained in the 2 to 3 x ULN range. In the remaining 18 participants, the ALT levels progressed to greater than 3 x ULN and these are the 18 participants described in the preceding paragraphs. Elevations between 2 and 3 x ULN were not predictive of progressive liver disease and thus not helpful as a monitoring tool.

There has been some discussion in the literature regarding combining elevated LFTs greater than 3 x ULN (either ALT or AST) with concurrently elevated total bilirubin greater than 2 x ULN for improved specificity and sensitivity of detecting clinically significant liver disease. In AFCAPS/TexCAPS, there were only 4 lovastatin patients who had liver chemistry elevations meeting the above criteria. The concurrent elevations in total bilirubin and LFTs experienced by these four patients were all single occurrences. In 3 of the 4 patients, the elevations resolved at follow up testing. One patient discontinued and was not retested. Notably, all 4 patients had a concurrent elevation in alkaline phosphatase (ranging from ~1.1 to 3 x ULN). These cases, therefore, are not technically consistent with “Hy’s Rule” which excludes events with clinically significant increases in alkaline phosphatase [81] since this may signify biliary obstruction as opposed to hepatocellular injury. As noted, three of the lovastatin-treated patients were diagnosed with cholelithiasis and the other with obstructive jaundice. In the placebo

group, 5 patients had elevated LFTs greater than 3 x ULN concurrently with total bilirubin greater than 2 x ULN. One patient had chronic active hepatitis, one patient had hepatitis A, two had cholecystitis, and one had colorectal cancer metastatic to the liver. Thus even using these more stringent criteria, there is no evidence of serious hepatotoxicity occurring in patients on lovastatin.

4.1.3 Postmarketing Spontaneous Reports

A review of selected hepatobiliary adverse experiences was conducted among postmarketing reports received from health care professionals and entered into Merck's Pharmacovigilance (Worldwide Adverse Experience System; WAES) database.

A few cases of liver failure and clinical hepatitis have been reported during postmarketing use with lovastatin. As of 01-Nov-2003 there were a total of 25 cases of hepatic failure/hepatic necrosis and 251 reports of "hepatitis" in the Merck WAES database reported by a health care professional, not all of which could be attributed to lovastatin (Note: Five of these reports included both adverse experiences of hepatic failure/necrosis and hepatitis). Even with a conservative approach that all these cases were causally related to lovastatin, with an estimated worldwide exposure to lovastatin of over 27 million patient-years, these figures give a reporting rate of acute liver failure and hepatitis of ~1.0 and 10.4 reports, respectively, per million patient-years of treatment. These numbers indicate that, even if all cases were assumed to be caused by lovastatin, the reporting of these events is extremely rare (it is important to note that under-reporting can be a limitation of spontaneous data).

There are ~2,000 cases of acute liver failure in the US per year [82]. The worldwide incidence of acute liver failure is on the order of 1 to 10 cases per million population per year [83]. Furthermore, the rate of hepatitis for nonsteroidal anti-inflammatory drugs is between 22 and 500 per 1 million patient years [84]. Therefore, based on the reporting rates, the risk of hepatic failure/hepatic necrosis or hepatitis is very small considering the vast number of patients exposed to lovastatin.

4.1.4 Published Clinical Literature

The most common type of hepatobiliary adverse reaction in patients taking statins, including lovastatin, is elevation of hepatic aminotransferases or transaminases. Elevation of transaminases associated with statin use is usually asymptomatic, dose-related, and transient. Acute liver failure associated with use of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, on the other hand, is a very rare event. The reporting rate is 1 in 1.4 million lovastatin patient treatment-years, similar to the background rate for idiopathic acute liver failure [54]. It is important to note that no relationship has been established between minor ALT elevations with statin use and hepatic failure [85].

Published reviews and commentaries by clinical experts concur that periodic monitoring of liver function tests does not predict progression to hepatic failure [54; 86]. The consensus expressed in the literature is that lovastatin does not pose a significant risk of hepatic injury.

The incidence of persistent elevations of ALT and/or AST >3x ULN ranged from 0 to 1.2% in patients taking various doses of lovastatin over a range of treatment durations in randomized, controlled trials. In most published studies, lovastatin dose was titrated so the incidence of LFT abnormalities with a specific dose cannot be determined. In studies where a fixed dose was administered, the incidence of LFT abnormalities was low for lovastatin doses of 20 mg or less. Regardless, transaminase elevation with lovastatin appears to be a benign and transient event even with continuation of therapy.

According to established criteria for screening tests, routine monitoring of hepatic enzymes appears to be unnecessary and ineffective. It may discourage use of lovastatin in a patient population where the benefit of LDL-cholesterol lowering far outweighs any risk posed by asymptomatic ALT elevation. Since transaminase elevation is a dose-related phenomenon, liver function monitoring would be even less useful for patients taking the proposed lovastatin 20-mg OTC product.

4.1.5 Safety of Statins in Patients With Elevated Liver Enzymes

A retrospective cohort study was conducted by investigators at the Indiana University School of Medicine [14] to assess whether patients with baseline elevations of serum transaminases have a higher risk of hepatic injury with statin treatment. The study compared 3 patient cohorts identified from data collected from a large academic medical practice, using the Regenstrief Medical Record System (RMRS). Cohort 1 consisted of hyperlipidemic patients with elevated baseline liver enzymes who were prescribed a statin. Cohort 2 consisted of hyperlipidemic patients with normal baseline enzymes who were prescribed a statin. Cohort 3 consisted of patients with elevated liver enzymes who were not prescribed a statin, but had follow-up ALT and/or AST values measured within the next 6 months. Patients with evidence of alcohol abuse, hepatitis B surface antigen, or hepatitis C antibody were excluded. Thus, the etiology of the increased LFTs was most likely due to undiagnosed nonalcoholic fatty liver disease, which is prevalent in the hyperlipidemic population.

The primary study endpoint was elevation of liver biochemistry values during the 6-month follow-up period, categorized as mild/moderate or severe. “Mild/moderate” elevations in liver biochemistries were defined as elevations of AST and/or ALT up to 10 times ULN in patients with normal baseline enzymes or up to 10-fold elevations from baseline values in patients with elevated liver enzymes at baseline. “Severe” elevations were defined as: (1) the development of serum bilirubin >3 mg/dL (regardless of baseline transaminases); or (2) elevations of AST and/or ALT greater than 10 times ULN in patients with normal baseline enzymes or >10-fold elevations from baseline values in patients with elevated liver enzymes at baseline.

The primary results of the study are presented in Table E-9 for the incidence of elevations in liver biochemistries in the 3 cohorts. Among patients who were prescribed statins (Cohorts 1 and 2), individuals with baseline enzyme elevations (Cohort 1) had a higher incidence of mild/moderate elevations during the study compared with patients with normal liver biochemistries at baseline (Cohort 2) (4.7% vs. 1.9%, p=0.002). However, there was no difference in the incidence of severe elevations between these 2 groups (0.6% vs. 0.2%, p=0.2).

More importantly, for those patients who had elevations of liver enzymes at baseline (Cohorts 1 and 3), there was no difference in liver biochemistries between the patients who received a statin (Cohort 1) compared with those who did not (Cohort 3). This was true for both mild/moderate elevations (4.7% vs. 6.4%, p=0.2) or severe elevations (0.6% vs. 0.4%, p=0.6).

Table E-9

Frequency of Varying Degrees of Elevations in Liver Biochemistries
Over a 6-Month Period in 3 Study Cohorts

	Cohort 1 (n=342)	Cohort 2 (n=1437)	Cohort 3 (n=2245)	p-Values	
				Cohort 1 vs. Cohort 2	Cohort 1 vs. Cohort 3
Mild/moderate elevations	4.7%	1.9%	6.4%	p=0.002	p=0.2
Severe elevations	0.6%	0.2%	0.4%	p=0.2	p=0.6

Cohort 1: Individuals with elevated baseline liver enzymes who were placed on a statin;
Cohort 2: Individuals with normal baseline liver enzymes who were placed on a statin;
Cohort 3: Individuals with elevated liver enzymes, but not placed on a statin.

[14]

To confirm these observations, Cohort 1 was also compared with 2 additional control groups. One of these was a sub-group of Cohort 3 patients who were age and gender matched to Cohort 1 (n=326). Their frequency of mild/moderate elevations (6.1%, p=0.4) or severe elevations (0.9%, p=0.6) was not significantly different than that of Cohort 1. The other additional control group consisted of 1,111 individuals with detectable hepatitis C antibody (not treated with statins or interferon), who had elevated baseline AST or ALT and a minimum of 2 or more follow-up AST or ALT values during the study period. Compared to Cohort 1, individuals in the hepatitis C control group had significantly higher frequency of mild-moderate (11.1%, p<0.001) or severe elevations (5.9%, p<0.001) in liver biochemistries.

Additional results from the study showed that statin discontinuation was similar between those patients with baseline elevations and those with normal baseline values (Cohort 1 vs. Cohort 2; 11.1% vs. 10.7%, p=0.8).

Furthermore, the study found that there was no difference among the specific statins used for the following parameters: the proportion of patients developing elevations in liver enzymes; mean change in AST or ALT values; or the proportion discontinuing the statin during the follow-up period. In this study, atorvastatin (46%) and simvastatin (51%) were the two most commonly prescribed statins. Additionally, there was no statistical difference in the incidence of liver enzyme elevations between the patients who received the median statin dose and those who received more than the median dose. The incidence of mild/moderate elevations in liver biochemistries in patients prescribed the median statin dose versus those prescribed higher doses was 2.5% and 2.9%, respectively (p=0.6). Similarly, the incidence of severe elevations in liver biochemistries in patients on median and on higher statin doses was 0.3% and 0.3%, respectively (p=0.9).

The study also assessed the extent to which practicing physicians comply with recommendations to obtain baseline liver chemistries prior to statin use. The proportion of patients in whom transaminases levels were available within 6 months prior to starting a statin were 58% in Year 1998, 57% in Year 1999, 58% in Year 2000, 66% in Year 2001, and 63% in Year 2002. Notably, patients who did not have baseline liver enzymes available prior to starting statins were similar to those who did have values available, with respect to the following outcomes: proportion of patients that exhibited a serum bilirubin >3 mg/dL during the follow-up period and proportion of patients that discontinued statins during the follow-up period.

In summary, this study demonstrated that among patients with elevated baseline liver enzymes, subsequent mild/moderate or severe elevations were not significantly higher in patients who received a statin compared with patients who were not placed on statin therapy. The authors concluded that the study data suggest that individuals with elevated liver enzymes do not have increased susceptibility to hepatotoxicity from statins [14].

These findings were consistent with those of an additional retrospective study from the Indiana University School of Medicine [87] that examined the risk of hepatotoxicity specifically with lovastatin in patients with elevated baseline transaminases. Although the lovastatin-treated patient cohorts in this study were smaller than the statin-treated cohorts in the first retrospective study [14] (755 lovastatin-treated vs. 1,779 statin-treated patients), liver chemistries were assessed over a 12-month follow-up period, twice as long as in the statin study. In the lovastatin study, significant elevations were defined as the development of serum bilirubin >3 mg/dL or AST and/or ALT values >5 times ULN (for patients with normal baseline enzymes) or >5 times baseline (for those with elevated liver enzymes at baseline) [87]. Seven-hundred fifty five hyperlipidemic patients without any history of hepatitis B, hepatitis C or alcohol consumption were identified who were

prescribed lovastatin over an 11-year period. Among 135 hyperlipidemic patients with increased baseline AST or ALT who were prescribed lovastatin, 0.7% experienced significant elevations in liver biochemistries over a 12-month follow-up period, similar to the rate of "severe" elevations (0.6%) observed in the equivalent cohort in the statin retrospective study. This incidence was not different from that observed among the 620 patients without baseline elevations who were prescribed lovastatin, where 0.3% developed significant elevations in liver enzymes during the follow-up period. No lovastatin-treated patient developed a bilirubin value >3 mg/dL and no cases met Hy's rule [elevated LFTs >3 x ULN (either ALT or AST) and concurrently elevated total bilirubin >2 x ULN, without significant alkaline phosphatase elevation]. Further, among 2,644 matched controls with elevated transaminases (without any history of hepatitis B, hepatitis C or alcohol consumption) who were not prescribed lovastatin, the incidence of significant elevations in liver biochemistries was 6.8%, with 3 of these patients (0.1%) having a follow-up bilirubin value >3 mg/dL. Thus, these results confirm the findings of the statin retrospective study [14] and provide additional evidence that treatment with lovastatin does not appear to increase the risk of hepatotoxicity in patients with baseline transaminase elevations [87].

4.1.6 Utility of Liver Function Test Monitoring

The utility of periodic liver function testing to help prevent hepatic injury among users of lovastatin 20 mg or less may be evaluated by established criteria for judging the appropriateness of using a given test to screen for a specific disease. Any such test should be effective in reducing morbidity or mortality and sufficiently accurate to avoid large numbers of false-positive and false-negative results. Mandated periodic liver function testing among users of lovastatin 20 mg or less cannot be justified by either of these two criteria. Extensive marketing experience shows that serious hepatic injury with lovastatin use is extremely rare. It is by no means evident that periodic monitoring of transaminases could have prevented these cases. Further evidence suggests that for the most part, physicians do not adhere to the LFT monitoring guidelines set forth in HMG-CoA reductase inhibitor labeling. Despite the fact that they do not perform liver function testing as recommended, liver toxicity with lovastatin use is extremely rare [88].

Elevated transaminases >3 x ULN occurred in a dose-related manner in clinical studies. During the 48 weeks of EXCEL, consecutive elevations >3 x ULN in ALT occurred in 0.1% of 1,639 placebo recipients and 0.1% of 1,625 lovastatin 20 mg daily recipients, increasing to 1.5% in 1628 users of lovastatin 40 mg b.i.d. [13]. None of the 8245 patients in that study had a 10-fold elevation in ALT.

During the 5 years of AFCAPS/TexCAPS, ~100,000 ALT and AST tests were performed, but there were only 29 elevations >3 x ULN in 6,605 participants. Elevations >3 x ULN in ALT confirmed upon re-testing occurred in 11 (0.3%) of 3248 placebo recipients and in 17 (0.5%) of 3242 lovastatin recipients [7]. Confirmed elevations >10 x ULN occurred in 3 (0.1%) of the placebo recipients and in 6 (0.2%) of the lovastatin recipients. In only one of the lovastatin patients and in two of the placebo patients was there a positive rechallenge [54].

These results indicate that sustained elevations in ALT were very uncommon among lovastatin users, especially at dose levels of 20-mg once daily or less. Furthermore, the elevations were not predictive of progressive lovastatin-related liver disease. Hepatic transaminase elevations occur in association with numerous other conditions including viral hepatitis, alcohol use, obesity, and exercise. Thus, the vast majority of hepatic transaminase elevations represent false-positive results from the standpoint of detecting any clinically relevant hepatic injury that may be related to use of lovastatin.

The rarity of serious hepatic injury such as liver failure in lovastatin-treated patients is also documented in the clinical literature. There is no documented case where such an injury could have been prevented by periodic monitoring of liver function tests. It has been estimated that the probability of detecting reversible liver failure with monthly liver enzyme testing is 0.0000064, while the rate of false positive results is greater than 82% and may be as high as 98% [54]. A study of 1,575 outpatients, 70.2% of whom, were on lovastatin, found no correlation between LFT monitoring and the risk of adverse events [89]. More commonly, such elevations have uncovered underlying conditions such as viral hepatitis, alcohol-related liver damage, or fatty liver associated with obesity or diabetes [54]. Therefore, the vast majority of hepatic transaminase elevations represent false-positive tests from the standpoint of detecting any hepatic injury that may be related to use of lovastatin. If false-positive results lead to discontinuation of lovastatin, the overall effect of monitoring may be to increase morbidity and mortality because of the lost benefit of LDL-cholesterol lowering.

4.1.7 Hepatobiliary Safety Summary

Lovastatin has been available for marketing for over 15 years with the equivalent of more than 27 million patient-years of therapy. The extensive safety data from lovastatin postmarketing database and the long term AFCAPS/TexCAPS study demonstrates little evidence of hepatotoxicity of the drug. There seems to be a dose response regarding abnormalities of LFTs as shown in the EXCEL trial, but doses less than 40 mg are not different from placebo. Further, 2 recent retrospective cohort studies have demonstrated that there does not appear to be an increased risk of hepatotoxicity with lovastatin or other statins in hyperlipidemic patients with baseline LFT abnormalities.

Given the high false-positive rates of LFT monitoring, clinically unimportant fluctuations of LFTs in this patient population, the inability of testing to predict serious hepatotoxicity, and the low incidence of hepatotoxicity, baseline testing and routine monitoring of LFTs in patients taking the OTC dose of lovastatin 20 mg is not necessary. This is especially true for patients who are relatively healthy with no history of liver disease, diabetes, or other significant medical illnesses. Furthermore, even in cases of undiagnosed liver disease, there is no evidence that low-dose lovastatin would cause further damage to the liver or exacerbation of the disease since it was not hepatotoxic based on extensive clinical data.

4.2 Myopathy

4.2.1 Introduction

Myopathy, and rhabdomyolysis in particular, may be considered the adverse experience of primary concern that is associated with HMG-CoA reductase inhibitors. However, clinical study and marketed lovastatin experience indicate that their occurrence is rare and dose related. In the context of clinical trials involving an inhibitor of HMG-CoA reductase, the term myopathy is often defined as unexplained muscle pain or weakness with a CK value >10 x ULN. It is generally a condition of sudden onset that has been reported most commonly within the first few weeks of treatment, or shortly after the introduction of an interacting drug with high doses of lovastatin, but sometimes myopathy occurs after several years of treatment for no obvious reason. If myopathy occurs, therapy should be discontinued promptly, whereupon there is usually a prompt recovery without sequelae. The term rhabdomyolysis is used to describe a severe form of myopathy that is associated with evidence of end-organ damage (usually renal damage with myoglobinuria) and often prompts hospitalization. The condition may, as a consequence of myoglobinuria, result in acute renal failure and death.

Myopathy is clearly a class effect, because it has been reported with all HMG-CoA reductase inhibitors. In rats, the myopathic effects can be prevented by mevalonate, the product of the inhibited enzyme [90]. The risk of myopathy with statin treatment is dose related. However, in clinical studies, the incidence of myopathy with the proposed nonprescription dose of lovastatin 20 mg was similar to that of placebo. The concomitant use of other lipid-lowering therapy increases the risk of myopathy, including lipid-lowering doses (≥1 g/day) of niacin (nicotinic acid) and fibrates, particularly gemfibrozil [91; 92; 93]. Both fibrates and niacin can cause myopathy when given alone [94; 95]. There is currently no adequate explanation for why 3 classes of lipid-lowering drugs (HMG-CoA reductase inhibitors, fibrates, and niacin) that have quite different pharmacologic properties can all cause myopathy. The mechanism by which any of these drugs cause myopathy is not well understood. In the case of concomitant use of lovastatin and gemfibrozil, recent evidence indicates that gemfibrozil inhibits statin acid glucuronidation, suggesting that there is a major pharmacokinetic component to this interaction [96; 97].

Lovastatin and some of the other HMG-CoA reductase inhibitors are metabolized by cytochrome P-450 3A4 (CYP3A4). Clinical experience has shown that the risk of myopathy with lovastatin is increased by concomitant use of drugs that strongly inhibit CYP3A4 at therapeutic doses (i.e., cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, and nefazodone) [79]. In addition, the risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class [98]. Drug-drug interactions are discussed later in this Section. See Appendix H for the prescription MEVACOR™ package circular.

4.2.2 Clinical Studies

EXCEL

As noted earlier, EXCEL was a 48-week, placebo-controlled study using lovastatin doses of 20 mg to 80 mg/day. Myopathy, defined as muscle symptoms associated with an increase in CK to >10 x ULN, occurred in 5/6,582 (0.08%) patients receiving treatment with lovastatin (4 patients receiving 80 mg [0.2%], 1 patient receiving 40 mg every evening [0.1%], and none of the 1,642 patients receiving lovastatin 20 mg). The maximum CK levels in the five patients ranged from 1,991 to 10,300 IU/L. Clinical signs and symptoms occurred within 3 to 23 weeks after study entry. Two of the 5 patients continued to receive lovastatin and completed the study while their symptoms resolved and their CK levels returned to normal. CK levels for the 3 discontinued patients decreased to normal and symptoms resolved within 30 days of discontinuing lovastatin. None of the patients experienced myoglobinuria or acute renal failure.

The incidence of muscle symptoms with any CK elevation above the ULN was similar in the groups receiving 20 or 40 mg of lovastatin per day and the placebo group. As seen in Table E-10, muscle symptoms, with or without any CK elevation, are relatively common in the population at large, and the majority are not drug-related.

Table E-10

Incidence of Muscle Symptoms (With and Without Creatine Kinase Elevations) and Creatine Kinase Elevations (With or Without Muscle Symptoms) in EXCEL

	Treatment Group				
	Lovastatin				Placebo N=1663
	20 mg every evening N=1642	40 mg every evening N=1645	20 mg twice daily N=1646	40 mg twice daily N=1649	
	n (%)†	n (%)†	n (%)†	n (%)†	n (%)†
Muscle symptoms with CK elevations					
CK >10 x ULN‡	0 (0.0)	1 (0.1)	0 (0.0)	4 (0.2)	0 (0.0)
Any CK elevation	35 (2.1)	17 (1.0)	26 (1.6)	58 (3.5)	27 (1.6)
Muscle symptoms without CK elevations	102 (6.2)	94 (5.7)	90 (5.5)	95 (5.8)	98 (5.9)
CK elevations with or without muscle symptoms					
CK >10 x ULN	3 (0.2)	3 (0.2)	3 (0.2)	8 (0.5)	7 (0.4)
Any CK elevation	473 (28.8)	491 (29.8)	525 (31.9)	572 (34.7)	480 (28.9)

† Percentages refer to patients randomized. ULN indicates upper limit of normal CK values (190 and 235 IU/L for women and men, respectively); q.p.m., once daily with the evening meal; and b.i.d. twice daily.

‡ Preplanned comparison; incidence was too low to test for trend with daily doses of lovastatin.

CK = Creatine kinase; ULN = Upper limits of normal.

AFCAPS/TexCAPS

In this trial during which participants were taking lovastatin or placebo for over 5 years, CK elevations >10 x ULN were reported in 0.6% of the cohort: 21 receiving lovastatin 20 to 40 mg daily and 21 receiving placebo. Among the 3304 receiving lovastatin, the only case of symptomatic myopathy was one case of rhabdomyolysis. The episode of rhabdomyolysis occurred postoperatively following surgery for prostate cancer and was determined to be unrelated to treatment with lovastatin 20 mg (the participant discontinued drug upon hospital admission and restarted lovastatin without a recurrence of symptoms). Two cases of rhabdomyolysis were reported among the participants treated with placebo [7].

4.2.3 Postmarketing Spontaneous Reports

The WAES database of postmarketing adverse experience reports was searched for all reports from health care professionals (HCPs) carrying a MedDRA preferred term of: myopathy, muscle disorder NOS, myopathy toxic, myositis, myositis-like syndrome, polymyositis, rhabdomyolysis, myoglobin urine present, myoglobinuria, or blood myoglobin increased. Since first approval through 01-Nov-2003, 875 reports with reported events mapping to one or more of these adverse experience terms were recorded. Given an estimated worldwide exposure to lovastatin of ~27 million patient-treatment years, this represents a reporting rate of myopathy of ~3 per 100,000 patient-treatment years. Of the 875 reports of muscle adverse experiences, 336 (38%) included an adverse experience term of rhabdomyolysis, myoglobinuria, myoglobin urine present, or blood myoglobin increased, and are referred to in this summary as cases of “rhabdomyolysis.” The remaining 539 (62%) reports included one or more of the 7 terms possibly indicative of less severe forms of myopathy (myopathy, muscle disorder NOS, myopathy toxic, myositis, myositis-like syndrome, polymyositis), asymptomatic increased CPK, and are referred to as cases of “other myopathy” (Table E-11).

Table E-11

Spontaneous Reports of Rhabdomyolysis or Other Myopathy in Patients With and Without Concomitant Medications Known to Increase the Risk of Lovastatin-Associated Myopathy (WAES)

	Rhabdomyolysis		Other Myopathy	
	Reports† (N=336)	Deaths (n=26)	Reports† (N=539)	Deaths (n=8)
With interacting concomitant medication‡	188	15	100	2
Any strong CYP3A4 inhibitor	70	5	17	0
Cyclosporine	34	3	7	0
Erythromycin/clarithromycin	23	2	6	0
Itraconazole/ketoconazole	11	1	2	0
HIV protease inhibitor	1	0	0	0
Nefazodone	3	0	2	0
Mibefradil	3	0	2	0
Any moderate CYP3A4 inhibitor	24	4	15	0
Amiodarone	1	1	1	0
Verapamil	23	3	14	0
Niacin/nicotinic acid	34	3	28	1
Any fibrate	97	9	50	1
Benzafibrate	0	0	1	0
Fenofibrate	1	0	1	0
Gemfibrozil	96	9	48	1
Without interacting concomitant medication	148	11	439	6

† Includes both fatal and nonfatal reports.
‡ Patients may have been taking more than 1 interacting concomitant medication. The same patient may appear in more than 1 category of interacting concomitant medications.
WAES = Worldwide Adverse Experience System.

Rhabdomyolysis/Myoglobinuria

The 336 reports of rhabdomyolysis represent a reporting rate of ~1.2 per 100,000 patient-treatment years. Information about concomitant medications is contained in 281 of the reports. Of the 336 reports, 188 (56%) involved patients who received concomitant medication with one or more drugs recognized to increase the risk of rhabdomyolysis in patients treated with lovastatin. The potentially interacting drugs noted as concomitant medication in these 188 reports are detailed in Table E-11. Fatal outcome was reported in 15 (8%) of the 188 cases. See below for reports of rhabdomyolysis or myopathy with fatal outcomes.

In 148 (44%) of the 336 reports of rhabdomyolysis there was no information regarding concomitant use of medication known to increase the risk of rhabdomyolysis in patients treated with lovastatin. These 148 reports represent a reporting rate of rhabdomyolysis in the absence of interacting medications of 0.53 per 100,000 total patient-treatment years. The outcome was death in 11 (7%) of the 148 cases.

Myopathies Without Rhabdomyolysis

The 539 reports of myopathy without rhabdomyolysis included 100 (19%) in which concomitant medication with one or more drugs known to increase the risk of myopathy in patients treated with lovastatin was noted (see Table E-11). Fatal outcome was reported in 2 (2%) of the 100 cases.

In 439 (81%) of the reports of myopathy without rhabdomyolysis, no concomitant medication with a drug known to increase the risk of lovastatin-associated myopathy was reported. Fatal outcome was reported in 6 (1.4%) of the 439 cases; 4 of these cases had a cause of death more likely than myopathy.

Reports of Rhabdomyolysis or Myopathy With Fatal Outcome

A total of 34 deaths were reported in patients who experienced rhabdomyolysis or other myopathy. It should be noted that various causes of death were recorded in these cases and that some deaths may not be attributable to rhabdomyolysis or myopathy. In addition, most of these reports involved patients with significant pre-existing co-morbidities and chronic health conditions.

In 8 of the 34 cases, death was likely the result of one or more serious co-morbid conditions rather than the adverse experiences of rhabdomyolysis or myopathy. Probable causes of death in these cases included cardiac events, bacterial sepsis, pulmonary hypertension, herpetic pneumonia, disseminated intravascular coagulation, intestinal infarction, pre-existing polymyositis, pulmonary embolism, and lung carcinoma.

In 17 other cases, rhabdomyolysis or myopathy may have contributed to the patient's death, but other causes were also implicated, including cardiovascular disease, pneumonia, pulmonary embolism, multi-organ failure, renal failure secondary to vascular disease, worsening of pre-existing renal failure, jaundice, disseminated fungal infection, bacterial sepsis, and gastrointestinal bleeding.

Myopathy, rhabdomyolysis, or rhabdomyolysis with renal failure was the only cause of death noted in 6 case reports, 5 of these reports specified rhabdomyolysis and 1 noted myopathy as the probable cause of death. Three of the patients who developed rhabdomyolysis were taking gemfibrozil or niacin. In the myopathy case, a patient taking lovastatin and unspecified heart medications was hospitalized after developing myopathy in her lower extremities; lovastatin was discontinued. The patient died 3 days after lovastatin was reinitiated. In general, very few details were provided in these 6 reports, precluding accurate case assessment.

The cause of death was unknown in 3 patients; one of these cases was a heart transplant patient receiving cyclosporine; another had suspected plutonium exposure. In the third case, the cause of death was unconfirmed but was possibly due to progressive polymyositis.

Most of the cases with fatal outcome involved patients with significant pre-existing and/or co-morbid conditions. In 26 of the 34 reports, the patients were known to have diabetes, heart disease, and/or renal impairment. Fourteen of the 26 patients were also known to be taking a medication that could increase the risk of myopathy. Of the 8 patients not known to have 1 of the above conditions, 1 patient was receiving chemotherapy for lung cancer, another had possible dermatomyositis, and 3 were taking niacin or gemfibrozil.

4.2.4 Relationship to Lovastatin Dose

Experience from clinical trials suggests that the risk of myopathy increases with lovastatin dose. While the incidence of myopathy with various lovastatin doses cannot be assessed from WAES data since accurate numerator and denominator data are not available, the number of myopathy reports that specified a dose can be evaluated in the context of the estimated patient exposure to various total daily doses. It is estimated that ~5.5% of patients on lovastatin received ≤10 mg daily, 63% received 20 mg, 28% received 40 mg, 0.3% received 60 mg, and 2.4% received ≥80 mg. An additional 1.1% of patients received 30 mg daily.

The risks of rhabdomyolysis and myopathy appear to be dose related. Table E-12 shows the number of reported cases per 100,000 patient-treatment years for the different doses of lovastatin. The number of reported cases per 100,000 patient-treatment years was based on the number of reports of rhabdomyolysis or myopathy in patients without concomitant medications known to increase the risk of myopathy. It should be noted that the estimated patient-treatment years have not been adjusted downward to take these concomitant medications into account. Compared with the 20-mg dose, the number of reports of rhabdomyolysis per 100,000 patient-treatment years was ~12 times greater with doses ≥80 mg/day. The number of reports of myopathy per 100,000 patient-treatment years was ~3 times greater with doses ≥80 mg/day than with 20 mg/day. As stated previously, there are significant limitations with the analysis of postmarketing reports. Nonetheless, these data suggest that there is a dose relationship among postmarketing reports of rhabdomyolysis and myopathy, which is consistent with clinical trial experience for lovastatin.

Table E-12

Spontaneous Reports of Rhabdomyolysis or Myopathy in Patients Without Concomitant Medications Known to Increase the Risk of Lovastatin-Associated Myopathy Per 100,000 Patient-Treatment Years by Total Daily Dose of Lovastatin (WAES)

	Total Daily Dose of Lovastatin			
	≤10 mg	20 mg	40 mg	≥80 mg
Estimated Percent of Usage†	5.5%	63%	28%	2.4%
Estimated patient Treatment years (PTY) Based on percent of usage	1,511,856	17,317,627	7,696,723	659,719
Reported cases of Rhabdomyolysis for 100,000 PTY	0	0.22	0.42	2.6
Reported cases of myopathy other than rhabdomyolysis per 100,000 PTY	0.26	1.1	0.77	3.2

† Based on prescription volume from IMS Health (US only).
WAES = Worldwide Adverse Experience System; IMS = Intercontinental Marketing Services.

4.2.5 Published Clinical Literature

The scope of the literature on this topic reflects the many years of experience with lovastatin and other HMG-CoA reductase inhibitors (statins). A number of reviews of this topic have been published in the last 3 years (2001 to 2003) [99; 100; 101; 51; 102]. In addition, a Clinical Advisory on statins was issued by the American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute in 2002 [5]. These publications concur that there is a risk of myopathy with any currently marketed HMG-CoA reductase inhibitor, but that rhabdomyolysis is a rare event that occurs much less frequently during treatment with currently marketed statins than with cerivastatin, which has been withdrawn from marketing. Agreement also exists that the risk of myopathy, which increases with dose and with co-administration of certain drugs utilizing the same metabolic pathway, is outweighed by the demonstrated clinical benefit of a reduction in cardiovascular events in patients treated with HMG-CoA reductase inhibitors [103; 51; 53]. While encouraging "appropriate caution" in certain patients, the Clinical Advisory paper commented on under-use of statins in clinical practice [5].

The incidence of myopathy is generally similar for all currently available statins and ranges from 0.1% to 0.5% with monotherapy [104; 105]. Other reviews confirm a similar 0.1% to 0.5% incidence of myopathy (defined as symptoms plus serum creatine kinase [CK] increase of at least 10 times upper limit of normal) specifically with lovastatin[106; 107; 108; 109; 110]. Given that this experience with lovastatin includes a broad range of patients, it is likely that the incidence of myopathy in a relatively healthy population choosing low-dose OTC treatment will be even lower.

Factors that increase the risk of myopathy with HMG-CoA reductase inhibitor therapy have been well-defined, allowing for more accurate risk management in an OTC setting. Combination therapy with 2 or more lipid-lowering drugs increases the risk of myopathy to 0.5 to 2.5% [105] or as many as 1 in 20 patients treated with combination lovastatin and gemfibrozil [111; 112; 92].

Few cases of myopathy progress to rhabdomyolysis [113], and severe rhabdomyolysis with renal failure is an even rarer occurrence [114; 115], particularly in patients receiving a lovastatin dose of 20 mg/day.

4.2.6 Myopathy Summary and Conclusions

In EXCEL, myopathy occurred in 1 case (0.03%) with 40 mg/day and in 4 cases (0.2%) with 80 mg daily; there were no cases of myopathy with 20 mg/day. In AFCAPS/TexCAPS, there were no cases of symptomatic myopathy except for 1 case of rhabdomyolysis among the 3,304 (0.03%) patients on treatment with lovastatin (which occurred postoperatively) and 2 cases of rhabdomyolysis among 3,301 (0.06%) placebo-treated participants. In clinical trials, the incidence of myopathy in those receiving lovastatin 20 mg daily is similar to that reported for those taking placebo. The number of myopathy cases found in spontaneous reports from healthcare professionals is very small given the extensive exposure to lovastatin in marketed use. Review of the extensive literature concerning lovastatin and myopathy supports the conclusion that the risk of myopathy with a 20-mg dose of lovastatin OTC in the target population is very low. Taken together, available data from large clinical trials, spontaneous reports, and published literature support the following conclusions:

- The risk of myopathy or rhabdomyolysis with lovastatin is low and dose related. In clinical trials, the incidences of these adverse experiences with a 20-mg dose were no different than placebo. The risk may increase when used with strong CYP3A4 inhibitors.
- The number of myopathy cases found in spontaneous reports from healthcare professionals is very small given the extensive exposure to lovastatin in marketed use.
- Myopathy is a symptomatic condition that can be recognized by patients and addressed in the label. The condition virtually always resolves after discontinuation of the drug.

4.3 Drug-Drug Interactions

4.3.1 Other Lipid-lowering Medications

Monotherapy with fibrates and, to a lesser extent, niacin, is occasionally associated with myopathy. Concomitant use of fibrates or niacin may increase the risk of myopathy in patients taking any of the HMG-CoA reductase inhibitors (statins).

Niacin has not been shown to alter plasma levels of lovastatin. The increased risk of myopathy appears to be related to the additive lipid-lowering effect of this agent. In postmarketing experience, there were 34 spontaneous reports of rhabdomyolysis in patients taking niacin with lovastatin (mostly doses ≥1 g/day).

Fibrates may interact with lovastatin through a pharmacodynamic mechanism. However, in the case of gemfibrozil, the interaction has been shown to be at least partially pharmacokinetic via inhibition of glucuronidation. Fibrates were the most commonly reported potentially-interacting drugs among spontaneous reports of rhabdomyolysis in patients taking lovastatin (99 of 340 reports).

4.3.2 CYP3A4 and Other Pharmacokinetic Interactions

Lovastatin is not known to affect the plasma concentration of any other drugs. Lovastatin is not an inhibitor of cytochrome P-450 3A4 (CYP3A4) in humans at the recommended clinical doses.

Many medications, including lovastatin, are metabolized by CYP3A4. CYP3A4 inhibitors have been shown to increase plasma concentrations of HMG-CoA reductase inhibitory activity in patients taking lovastatin. Potent inhibitors of CYP3A4 taken concomitantly with lovastatin have been reported to increase risk of myopathy.

While spontaneous reports provide a signal of increased relative risk in patients taking lovastatin and a potent CYP3A4 inhibitor, AFCAPS/TexCAPS shows that the risk is actually quite low. In AFCAPS/TexCAPS, concomitant use of lovastatin and potent CYP3A4 inhibitors was not associated with increased frequencies of myopathy or myalgia (Table E-13). There were 1,046 patients who took 1 or more strong CYP3A4 inhibitors (erythromycin, clarithromycin, ketoconazole, itraconazole, nefazodone) during the study. The incidence of musculoskeletal adverse experiences in general, and myalgia in particular, were not significantly greater in patients taking potent inhibitors with concomitant lovastatin versus those receiving placebo. There were no cases of myopathy or rhabdomyolysis in the 535 patients taking lovastatin who also took a potent CYP3A4 inhibitor. AFCAPS/TexCAPS provides evidence that with lovastatin 20 to 40 mg daily, the frequency of muscle symptoms is not appreciably increased with concomitant use of potent inhibitors such as erythromycin.

Table E-13

Selected Adverse Experiences[†] in Patients Taking Concomitant Strong CYP3A4 Inhibitors
AFCAPS/TexCAPS (N=6605)

Adverse Experience	Lovastatin 20 to 40 mg (N=535[‡])		Placebo (N=512[§])	
	n	(%)	n	(%)
Any musculoskeletal adverse experiences	42	(8)	39	(8)
Myalgia	3	(1)	4	(1)
Muscle weakness	1	(0.2)	2	(0.4)
Myopathy/rhabdomyolysis	0	(0)	0	(0)

[†] Table presents only adverse experiences that were serious, drug-related, or caused discontinuation.
[‡] Erythromycin (379), clarithromycin (107), ketoconazole (42), itraconazole (51), nefazodone (4)
[§] Erythromycin (370), clarithromycin (110), ketoconazole (21), itraconazole (42), nefazodone (5)

Patients may have been taking one or more of these concomitant medications.

4.3.3 Drug-Drug Interactions —Summary and Conclusions

Lovastatin OTC should not be used with potentially interacting drugs including itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, cyclosporine, gemfibrozil, and niacin. Since first approval through 1-Nov-2003 there were 83 reports from health care professionals of "drug interactions" with the above-mentioned drugs known to have a potential interaction with lovastatin. In comparison, there were 288 reports of myopathy where patients were reported to be taking interacting concomitant medications. Even considering the larger number of reports, with an estimated worldwide exposure to lovastatin of over 27 million patient-years, these figures give a reporting rate of drug interactions with drugs known to have a potential interaction with lovastatin of ~1.0 reports per 100,000 patient-years of treatment. The data from AFCAPS/TexCAPS suggests that concomitant use of an interacting drug with low doses of lovastatin is no more likely to result in an adverse event than with the interacting drug taken alone.

Nonetheless, in rare instances, the consequences of potential drug interactions can be serious. Therefore, the MEVACOR™ OTC label is used to convey simple warning messages reinforced multiple times and places. In addition, the package insert lists the specific interacting medications that should be avoided. The ability of consumers to comprehend that they should not use lovastatin concomitantly with any other prescription drugs before checking with a health care professional was evaluated in the CUSTOM study and is addressed in detail in the Consumer Behavior Section of this submission.

Based on review of the available data, the following conclusions can be drawn regarding lovastatin and drug interactions:

- Concomitant use of other lipid-lowering agents (gemfibrozil and niacin) increases the risk of myopathy. The interaction between lovastatin and gemfibrozil appears to be at least partially pharmacokinetic, whereas niacin has not been shown to alter plasma levels of lovastatin.
- Concomitant treatment with strong CYP3A4 inhibitors increases plasma HMG-CoA reductase inhibitory activity levels, and therefore may increase an individual's risk of myopathy.
- The risk of myopathy appears to be low at the proposed OTC dose of lovastatin 20 mg/day, even with concomitant use of a strong CYP3A4 inhibitor.

4.4 Drug-Disease Interactions

Published clinical studies contain information about the safety of lovastatin when used by patients with common medical conditions such as hypertension and diabetes mellitus. Selected studies are discussed below.

4.4.1 Hypertension

Hypertension and hypercholesterolemia frequently coexist. The efficacy and safety of lovastatin in patients with hypertension was evaluated in a subgroup analysis of EXCEL [116]. There was no attenuation in the lipid-altering efficacy of lovastatin when administered in patients being treated concurrently with frequently administered antihypertensive drugs. There appeared to be no clinically important deterioration in the safety and tolerability profiles of lovastatin when taken with these drugs. Lovastatin did not have a clinically important effect on blood pressure in the all-patients-treated analysis. The mean changes from baseline for blood pressure were similar in the lovastatin and placebo groups. In the lovastatin groups, the largest mean change from baseline to the end of therapy was –1.3 mm Hg for systolic blood pressure and –0.7 mm Hg for diastolic blood pressure [13].

In a double-blind, placebo-controlled study conducted in 293 patients with mild-to-moderate hypertension, the addition of lovastatin to lisinopril or nifedipine therapy did not affect the antihypertensive efficacy of either drug and the therapies were generally well tolerated in combination [117]. Additionally, the reduction in serum cholesterol with combination therapy was similar in magnitude to that observed historically with lovastatin alone. A retrospective analysis of a multicenter, open, prospective study evaluated the efficacy and tolerability of lovastatin in 213 hypercholesterolemic hypertensive patients [118]. The authors concluded that lovastatin effectively improves lipid levels in these patients without affecting blood pressure control.

4.4.2 Diabetes Mellitus

The safety and tolerability of lovastatin in patients with noninsulin-dependent diabetes mellitus (NIDDM) has been examined in several small studies [119]. Lovastatin was effective in reducing LDL-C and was generally well tolerated. Lovastatin did not have a clinically important effect on fasting glucose or hemoglobin $A1_c$. The value of cholesterol lowering with the related drug simvastatin in patients with diabetes mellitus was examined in a subgroup analysis of 4S [120]. In that study, cholesterol lowering with simvastatin improved the prognosis of 202 diabetic patients with CHD. The risk of major coronary adverse experiences was reduced by 55% in the patients randomized to simvastatin (p=0.002).

4.4.3 Renal Disease

The prescription labeling for lovastatin advises that doses above 20 mg/day be used cautiously in patients with severe renal insufficiency (creatinine clearance <30 mL/min) [79]. This caution is based on the observation that cases of rhabdomyolysis have been reported in patients with severe renal impairment, and a clinical study has shown that plasma levels of total inhibitors after a single dose of lovastatin were ~2-fold higher than in healthy volunteers. Lovastatin is not known to directly affect renal function. In EXCEL, mean changes in serum creatinine were similar among the lovastatin and placebo groups. The effect of cholesterol-lowering therapy on the progression of diabetic nephropathy was studied in 34 patients with type II diabetes mellitus [121]. Changes in glomerular filtration rate over the 2-year study tended to be less in patients treated with lovastatin compared with those receiving placebo, supporting the position that lovastatin will not exacerbate underlying renal disease.

4.4.4 Liver Disease

Active liver disease tends to lower plasma cholesterol, and is itself a more urgent medical priority than reducing the need for lipid-lowering therapy. Like other inhibitors of HMG-CoA reductase, lovastatin produces asymptomatic increases in hepatic transaminases in some patients at higher doses. For these reasons, the prescription labeling for lovastatin states that active liver disease is a contraindication to treatment with the drug [79]. Therefore, clinical studies have not evaluated the safety of lovastatin in patients with active liver disease. There is no evidence that lovastatin exacerbates underlying active or inactive liver disease, and no evidence that lovastatin 20 mg is hepatotoxic. Nevertheless, as a conservative measure, in the proposed nonprescription lovastatin product circular, consumers with active liver disease are directed not to use the product.

4.4.5 Thyroid Disease

In a small number of patients with moderately elevated serum cholesterol (e.g., 200 to 240 mg/dL), the cholesterol elevation is due at least in part to other causes, principally subclinical hypothyroidism in women, and in a few patients, overt untreated hypothyroidism. Hypothyroidism is thought to account for about 2% of all cases of hyperlipidemia [122]. The effect of subclinical hypothyroidism on serum cholesterol is not large: in women, the estimated effect is ~19 mg/dL [123; 124]. Patients with hypothyroidism are frequently undiagnosed in the early stages of the disease and may choose to take nonprescription lovastatin. Thus, although these patients should still benefit from the reduction in LDL-C that lovastatin 20 mg will provide, there may be some concern that use of nonprescription lovastatin may delay diagnosis of the disease and appropriate treatment with thyroid hormone replacement therapy. However, because hypothyroidism is diagnosed on the basis of symptoms and thyroid function tests, and certainly not on the basis of elevated lipids, this argument seems more theoretical than real. Whether or not a hypothyroid patient takes lovastatin, progression of the disease will produce symptoms that are likely to lead to medical consultation. It is not likely that correction of moderate hyperlipidemia, a nonspecific and relatively unimportant manifestation of hypothyroidism, will materially delay diagnosis, given the wide variety of symptoms—well known to most practitioners—that the disease causes. Therefore, the availability of nonprescription lovastatin is unlikely to constitute a significant barrier to appropriate diagnosis and treatment.

4.4.6 Use in Elderly

The safety and tolerability of lovastatin in elderly patients has been examined in several small studies and post-hoc analyses. Compared with younger patients, elderly patients could be considered at increased risk of adverse reactions, particularly myopathy, with statin use since they are more likely to be taking other medications, have complicating medical conditions, and because drug metabolism may change with age [125; 126]. Published clinical studies, however, do not indicate a difference in tolerance associated with age. A placebo-controlled study in 431 patients 65 years or older found that lovastatin was extremely well tolerated in an older cohort [127]. In a retrospective analysis of a 6-month, open-label study, 144 elderly (age ≥65 years) patients had a similar incidence of adverse reactions as 343 younger patients [128].

A Merck study conducted in 141 patients ≥65 years of age with LDL-cholesterol above the 75th percentile demonstrated that lovastatin was generally well tolerated in elderly hypercholesterolemic patients treated for up to 1 year. Twenty-four of these patients were ≥75 years of age.

In a pharmacokinetic study including 16 elderly patients between 70 to 78 years of age, the mean plasma level of HMG-CoA reductase inhibitory activity was ~45% higher in this older cohort compared with patients between 18 to 30 years of age. However, clinical trial experience demonstrates that a dosage adjustment based on this pharmacokinetic difference is not needed. In AFCAPS/TexCAPS and EXCEL, 21% (3,094/14,850) of the combined patient population was ≥65 years of age and there was no overall difference in safety among older versus younger patients across the 20 to 80 mg/day dose range.

Post hoc analysis of the elderly subgroup in the AFCAPS/TexCAPS study also confirms that the risk of muscle toxicity does not seem to be increased in patients ≥65 years of age compared with younger patients (Table E-14). As noted previously, FDA agreed to a waiver from comprehensive reporting of adverse experiences in this 5-year study. Therefore, only adverse experiences that were serious, drug-related, or that caused discontinuation were reported in the Clinical Study Report and are summarized here. Within each age subgroup, there were no treatment group differences in the frequency of musculoskeletal adverse experiences (including myalgia). None of the elderly experienced myopathy (defined as muscle symptoms accompanied with CK elevations > 10 x ULN) or rhabdomyolysis. There were also no treatment group differences in the frequency of CK elevations >10 x ULN.

Table E-14

Number (%) of Patients With Muscle-Related Adverse Experiences (AEs)[†]
by Age (≥ and <65 Years) and by Treatment (AFCAPS/TexCAPS)

	Age ≥65 years		Age <65 years	
	Lovastatin (N=715)	Placebo (N=701)	Lovastatin (N=2589)	Placebo (N=2600)
Any musculoskeletal AE	68 (9.5)	54 (7.7)	181 (7.0)	167 (6.4)
Myalgia	4 (0.6)	5 (0.7)	18 (0.7)	22 (0.8)
Myopathy	0	0	0	0
Myositis	0	0	2 (0.1)	0
Muscle weakness	1 (0.1)	3 (0.4)	3 (0.1)	1 (0.04)
Rhabdomyolysis	0	0	1 (0.04)	2 (0.1)
CK > 10 x ULN[‡]	2/706 (0.3)	2/693 (0.3)	19/2537 (0.7)	19/2555 (0.7)

[†] Table presents only adverse experiences that were serious, drug-related, or caused discontinuation.
[‡] For the laboratory AE "CK > 10 x ULN," the denominator is the number of patients who underwent the laboratory test.
AFCAPS/TexCAPS = Air Force, Texas Coronary Atherosclerosis Prevention Study; CK = Creatine kinase; ULN = Upper limit of normal.

4.5 Drug Abuse and Overdose

The available data indicate that there is a wide margin of safety with lovastatin. In mice and rats, the acute LD_{50} values were >20 grams/kg and >5 grams/kg, respectively. From postmarketing reports of overdoses, the largest dose, 5 to 6 grams of lovastatin, was taken by a subject who had no specific symptoms and who fully recovered. From all sources, including the published literature, there have been no known reports of overdosage with a fatal outcome involving lovastatin as the sole agent.

The American Association of Poison Control Centers (AAPCC) collects data from poison control centers in at least 48 states and the District of Columbia and tabulates this information. During the 15-year period from 1988 through 2002, there were 4,612 exposures to lovastatin reported to poison control centers. Of the total exposures, 3,254 episodes involved lovastatin as a single agent. The outcome was death in 4 of the total 4,612 cases which involved lovastatin taken with other agents. There have been no fatal overdose exposure cases reported to AAPCC involving lovastatin as the sole agent. Symptom data were collected for 2,251 exposures to lovastatin alone. Symptoms were distributed across a number of body systems and there was no specific pattern.

In addition, lovastatin has occasionally been used in extremely high doses in studies evaluating its potential anti-tumor activity in cancer patients. In a Phase II study, 16 patients with advanced gastric adenocarcinoma received lovastatin 35 mg/kg/day for 7 days. Gastrointestinal dysfunction was the most commonly observed adverse experience and mild myalgia and muscle weakness with increased CK levels was considered the most severe clinical toxicity. In another study of 88 patients with advanced solid tumors who were given dose-escalating 7-day courses ranging from 2 to 45 mg/kg/day, doses up to 25 mg/kg/day were well tolerated. Reversible myotoxicity (myalgia and muscle weakness) was the dose-limiting toxicity. Although limited, these data indicate a wide margin of safety for lovastatin dosed at 20 mg/day.

There are no published reports describing recreational use of lovastatin. There are no WAES reports where lovastatin was the primary suspect agent that could be construed as evidence of drug abuse. Based on the drug's pharmacological properties and the extensive knowledge of the drug's clinical adverse experience profile, there is no information to suggest that the drug has the potential to be abused.

4.6 Exposure During Pregnancy

4.6.1 Introduction

The current package circular for prescription MEVACOR™ states that lovastatin is contraindicated in women who are pregnant or breastfeeding. Lovastatin should be administered to women of childbearing potential only if they are highly unlikely to conceive. The MEVACOR™ OTC label will also state that the product should not be used during pregnancy and, further, that the product should only be used by women

55 years of age or older. The safety of these drugs during pregnancy has not been conclusively determined [129] and discontinuation of lipid-lowering drugs for the relatively short duration of pregnancy should have little or no impact on long-term benefits of therapy for hypercholesterolemia. While it may be possible to suspend drug treatment during pregnancy, fetuses of women taking these drugs to treat hypercholesterolemia may be exposed early in the first trimester, before recognition of pregnancy.

When administered at high doses to rats and mice, lovastatin and/or its pharmacologically active metabolites were shown to be associated with the development of skeletal malformations. Due to this and the fact that discontinuation of lipid-lowering drugs for the relatively short duration of pregnancy was not expected to have any impact on the long-term benefits of therapy with these drugs, Pregnancy Category X was designated for lovastatin [79]. It is notable that the doses causing skeletal malformations in animals were 700 times the maximum recommended dose in humans [130]. Furthermore, animal studies are not always predictive of either the occurrence or lack of occurrence of a teratogenic effect in human pregnancy [131].

More recent studies show that the fetal effects described above are caused indirectly by maternal toxicity associated with the high doses of lovastatin used in the original animal studies, rather than a direct result of fetal exposure [132]. These studies demonstrate that after eliminating maternal toxicity during gestation (by utilizing a continuous treatment regimen prior to mating and then throughout mating and gestation), no evidence of teratogenicity was observed. Furthermore, subcutaneous dosing of the dams during gestation also eliminates the maternal toxicity and also resulted in an absence of teratogenicity. An assessment of maternal and fetal lovastatin plasma concentrations showed that the exposures of both dam and fetus were similar in all studies independent of the presence or absence of skeletal findings. In addition, fetal mevalonate concentrations were reduced to similar levels regardless of the treatment regimen utilized. Thus, mevalonate reductions were independent of the skeletal findings. All of the above data provide very strong evidence that the previously observed skeletal findings with lovastatin were due to excessive maternal toxicity and not a direct effect of the drug. Based on these studies, it is concluded that lovastatin is not teratogenic in rats even when administered at 800 mg/kg/day, a dose producing significant morbidity and mortality in dams. At this dose the safety margins based on plasma AUC values are ~26- and 90-fold, at the 80-mg/day and 20-mg/day doses, respectively.

To provide additional assurance of the safety of inadvertent human exposure to lovastatin during pregnancy a neonatal toxicity study of the active metabolite of lovastatin, L-154819, was conducted. This request was based upon the rationale that in rats a significant degree of neurological development occurs during the early postnatal period in this species, while in humans much of this development occurs prenatally. Results

showed no effects on body weight gain, behavior, neurological development, or histopathology at a dose of 10 mg/kg/day administered subcutaneously. At this dose plasma exposure margins are about 6-fold relative to human maternal exposures and likely significantly greater for fetal exposures. These data combined with the previously submitted negative developmental toxicity studies in rabbits show that at maximum-tolerated doses in both species there is no evidence for dose-related developmental toxicity.

4.6.2 Published Clinical Literature

Two articles [131; 133] were found that used computer-based systems to evaluate the teratogenic potential of various therapies, including lovastatin.

The first report by Lo and Friedman assessed the human teratogenic risk of 468 drugs approved by the FDA between 1980 and 2000 using the Teratogen Information System (TERIS), a computer-based clinical teratology resource [131]. TERIS risk classifications are determined by a consensus of opinion among an independent group of clinical teratologists. For the purposes of the study, the authors grouped the risk classifications into 3 broad categories: (1) no risk, minimal risk, or unlikely to produce an increased risk; (2) associated with a small, moderate, or high risk; or (3) risk undetermined. The main finding of the study was that the available data are inadequate to assess human teratogenic risk for most approved drugs (>90%), i.e., risk is "undetermined" for these treatments. Lovastatin had an "unlikely" TERIS risk rating and was among 6.4% of the treatments that were considered unlikely to pose a teratogenic risk in human pregnancy or had a rating of "minimal" or "none". An additional analysis of 163 drugs classified by both TERIS and the FDA Use-In-Pregnancy Categories showed a poor agreement between the systems. For example, lovastatin is categorized as unlikely to pose a teratologic risk according to TERIS, but the FDA Use-In-Pregnancy designation is Category X. This report equated the TERIS risk ratings system category of "none, minimal, or unlikely" to the FDA Use-In-Pregnancy Category of A or B. The lack of correlation between the 2 systems was not unexpected given that the FDA system is not intended to provide an estimate of teratogenic risk, even though it is often used in that manner in clinical practice. It was noted that the FDA categories take into account both benefit and risk of treatment during pregnancy, whereas the TERIS system assesses only risk of teratogenic effects and ratings are based only on published human data.

Another report investigated pregnancy outcomes following exposure to cholesterol-lowering agents by analyzing the Michigan Medicaid prospective surveillance of pregnancies linked to pediatric outcomes [133]. Among 229,000 records between 1985 and 1992, 11 outcomes were associated with lovastatin exposure at any time during pregnancy, with 3 exposures occurring during the first trimester. Only one of these outcomes included a diagnosis of a birth defect, described as a "cardiovascular defect." No further details were provided. It was noted that lovastatin was the most widely used cholesterol-lowering agent at that time.

Published case reports describing exposure to lovastatin during pregnancy are included in the Worldwide Adverse Experience System (WAES) database and are discussed in the following section.

4.6.3 Spontaneous Reports During Marketed Use

Postmarketing surveillance of lovastatin has included a systematic follow-up of reports of exposures during pregnancy. The pregnancy outcomes of women with exposure to lovastatin at various times during pregnancy have been examined based on reports submitted to Merck, as part of its ongoing worldwide monitoring of adverse experiences.

Methods

The WAES Database was searched to identify cases reported by both consumers and Health Care Professionals to Merck & Co., Inc. as exposures to lovastatin during pregnancy that were entered into the database from market introduction through 01-Jun-2003. The data obtained for these reports are not necessarily complete and may include unsubstantiated diagnoses and partial information. Attempts were made to follow-up all reports of exposure during pregnancy to identify the outcome of the pregnancy. Information is included in WAES whether the outcome is normal or abnormal, and regardless of the likelihood of a causal association. Although adverse pregnancy outcomes have been reported in pregnancies with lovastatin exposure, the reporting of these adverse experiences does not imply a causal association.

Reports in which pregnancy outcomes were known were categorized into one of the following outcomes: (a) congenital anomaly (occurrence of a structural defect in an embryo, fetus, stillborn or liveborn infant); (b) chromosomal abnormality; (c) spontaneous abortion (spontaneous miscarriage of conceptuses less than 20 weeks gestation from the first day of the last menstrual period [LMP]); (d) fetal death/stillbirth (non viability of conceptuses in pregnancies greater than or equal to 20 weeks gestation from LMP); and (e) live birth of a normal child.

Reports of exposure during pregnancy were classified as being prospective or retrospective. Prospective reports were all those for which notice of exposure was received prior to the outcome of the pregnancy being known. Retrospective reports were all those first received after the outcome of pregnancy was known. It is generally recognized that adverse pregnancy outcomes, particularly congenital anomalies, are likely to be disproportionately over-represented among retrospective reports [134]. Prospective reports, which are first submitted prior to any knowledge of pregnancy outcome, are less likely to be influenced by such reporting bias and more likely to reflect pregnancy outcomes in the exposed population as a whole. Thus, the incidence of pregnancy outcomes from prospective reports of lovastatin exposure during pregnancy can be compared to the incidence rates of pregnancy outcomes in the general population.

Results

A total of 105 reports of exposure to lovastatin during pregnancy were received from the time of market introduction to 01-Jun-2003. Of these reports, 67 were identified as prospective reports and 38 as retrospective reports.

Prospective Reports

Sixty-seven prospective reports of pregnancy in patients being treated with lovastatin were identified as having been received between the time of market introduction and 01-Jun-2003. Information on pregnancy outcome was available for 34 reports (50.7%) of patients.

Information on timing of exposure to lovastatin was available for all of the reports where outcome was reported. First trimester exposure was reported for 33 (97%) of these 34 cases.

The outcomes of these 34 pregnancies are summarized below (Table E-15). Three pregnancies were electively terminated. The rate of spontaneous abortion was 3% (1/31). There were 29 liveborn infants and 1 fetal death.

Table E-15

Pregnancy Outcomes for the 34 Prospective Reports of Patients Exposed to Lovastatin With Known Outcomes

Outcome	Number of Reports	Denominator	% Reports
Elective termination	3	34 †	9
Spontaneous abortion	1	31 ‡	3
Fetal death	1	30 §	3
Live births	29	31 ‡	94
Congenital anomalies	0	30 ‖	0

† Total number of pregnancies.
‡ Total number of spontaneous abortions and fetal deaths and live births (see methods for details).
§ Total number of fetal deaths and live births (see methods for details).
‖ Total number of fetal deaths and live births (see methods for details).

There were no reports of congenital anomalies in infants born to mothers who prospectively reported exposure to lovastatin during pregnancy.

Retrospective Reports

Retrospective reports are more difficult to interpret since usually only negative outcomes are more likely to be reported, and the total number of exposed pregnancies is not known. Thirty-eight retrospective reports of pregnancy in patients being treated with lovastatin were identified as being received between the time of market introduction and 01-Jun-2003. Information on pregnancy outcome was available for all 38 reports.

Information on timing of exposure to lovastatin was reported for 35 reports. First trimester exposure was reported in 33 (94%) of these 35 cases.

The outcomes of these 38 pregnancies are summarized in Table E-16. As explained above, incidence rates cannot be determined for retrospective reports. Eight pregnancies were electively terminated. There were 27 liveborn infants. No fetal deaths were reported.

Table E-16

Pregnancy Outcomes for the 38 Retrospective Reports of Patients Exposed to Lovastatin

Outcome	*N*
Elective termination	8
Spontaneous abortion	3
Fetal death	0
Live born	27
Congenital anomalies	7

Congenital anomalies were reported in 5 liveborn infants and in 2 electively aborted fetuses whose mothers were treated with lovastatin during pregnancy. These 2 reports of elective abortions appear to be descriptions of the same adverse experience. However, insufficient information is available to make that determination with certainty. First trimester exposure to lovastatin was reported in 6 of these 7 cases. The exposure was not reported in the other case. These reports are tabulated in Table E-17.

Table E-17

Retrospective Pregnancies: Reported Congenital Anomalies

Therapy (mg)	Age of Mother	Exposure (Gestational Week)	Outcome	Congenital Anomaly
Lovastatin 40 mg	22 years	0 to 5	Live birth 3400 g	Aortic hypoplasia, atrial septal defect, cerebral ventricular defect with secondary cerebral dysfunction. Liveborn infant with fatal outcome.
Lovastatin 10 mg	32 years	6 to 11	Female live birth	VATER‡ syndrome
Lovastatin 20 mg	24 years	0 to 18	Elective abortion	Neural tube defect
Lovastatin 40 mg	26 years	0 to 4	Female live birth 34 GW 1877 g	Skull defects described as Holoprosencephaly‖, limb deformities, skin tag (liveborn infant)
Lovastatin (dose unknown)	Unknown	Unknown	Live birth	"Severe deformities"
Lovastatin 20 mg	Unknown	1st trimester	Elective abortion	Spina bifida
Lovastatin 4 tablets (dosage unknown)	Unknown	0 to 8	Live birth	Small deformed right ear with no auditory canal

‡ Vertebral anomalies, anal atresia, tracheo-esophageal fistula with esophageal atresia, renal and radial dysplasia.
‖ Skull defects described as holoprosencephaly. MRI revealed hydrocephalus and aqueductal stenosis.

4.6.4 Postapproval Clinical Studies

EXCEL and AFCAPS/TexCAPS

As a result of the inclusion and exclusion criteria used for both EXCEL and AFCAPS/TexCAPS, there were no reported pregnancies during the course of either study.

4.6.5 Lovastatin Use During Pregnancy Summary and Conclusions

A review of the reports on lovastatin during pregnancy provides no prospective reports of congenital anomalies for lovastatin, and no pattern of anomalies among the retrospective reports. However, the number of prospectively reported cases with a known outcome that were available for analysis is small.

Drugs should be used during pregnancy only if the benefits of therapy clearly outweigh the risks. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little to no impact on the long-term risk associated with hypercholesterolemia. Therefore, nonprescription lovastatin will be indicated only for women ≥55 years of age and will be contraindicated in pregnancy. Treatment with lovastatin should be discontinued as soon as pregnancy is suspected and not resumed for the duration of pregnancy or until after it is confirmed that the woman is not pregnant.

5. Experience in an OTC Setting—Safety Results from CUSTOM Study

MEVACOR™ OTC (lovastatin 20 mg) was generally well tolerated in the OTC setting of the CUSTOM clinical study. Other than the unanticipated development of new drug allergy to lovastatin in one patient (with the development of a systemic-type allergic reaction), there were no other drug-related serious adverse events. Because there was no placebo or other control group in CUSTOM, a background rate for drug-related adverse events could not be established. However, historical data from comparative studies may be helpful in providing some context as discussed below.

The assessment of safety included 1061 patients who reported taking at least one dose of lovastatin 20 mg. Table E-18 summarizes the adverse experiences that occurred in the CUSTOM study. There were 28 (2.6%) patients who reported serious clinical adverse experiences, with only 1 of these patients having an adverse experience assessed as drug-related (hypersensitivity - a systemic-type allergic reaction as noted above). One patient died of cerebrovascular accident which was reported by the investigator as probably not related to study drug. There were no cases of myopathy, rhabdomyolysis, hepatitis, or hepatic failure.

Table E-18

Clinical Adverse Experience Summary
(CUSTOM Study)

	Lovastatin 20 mg (N=1061)	
	n	**(%)**
Number (%) of patients:		
With one or more clinical adverse experiences	452	(42.6)
With no clinical adverse experience	609	(57.4)
With drug-related clinical adverse experiences†	180	(17.0)
With serious clinical adverse experiences	28	(2.6)
With serious drug-related clinical adverse experiences†	1	(0.1)
Who died	1	(0.1)
Discontinued due to clinical adverse experiences‡	125	(11.8)
Discontinued due to drug-related clinical adverse experiences†	102	(9.6)
Discontinued due to serious clinical adverse experiences	7	(0.7)
Discontinued due to serious, drug-related clinical adverse experiences†	1	(0.1)

† Determined by the investigator to be possibly, probably, or definitely drug related.

‡ Patients who discontinued study therapy, but may or may not have discontinued from the study. (This group includes 108 patients who discontinued from the study because of a clinical adverse experience.)

There was a low incidence of clinical adverse experiences in each body system category except for Musculoskeletal Disorders. The most common types of clinical adverse experiences were those occurring in the Musculoskeletal System (17.3%). One hundred eighteen (11.1%) patients in CUSTOM reported myalgia, muscle weakness, or a closely-related adverse experience term. The most frequently reported specific adverse experiences were myalgia (7.0%), arthralgia (3.9%), and pain in extremity (2.0%). Also, there was a low incidence of drug-related clinical adverse experiences in each body system category except for Musculoskeletal Disorders (8.8%) and Gastrointestinal Disorders (5.4%). The most frequently reported drug-related clinical adverse experiences were myalgia (5.4%), flatulence (1.7%), arthralgia (1.5%), muscle weakness(1.1%) and diarrhea (1.0%). Table E-19 summarizes the drug-related clinical adverse experiences that had ≥1% incidence in CUSTOM.

Table E-19

Number (%) of Patients With Drug- Related† Clinical Adverse Experiences by Body System (Incidence ≥1%) (CUSTOM Study)

	Lovastatin 20 mg (N=1061)	
	n	**(%)**
Patients with one or more drug-related clinical adverse experience	180	(17.0)
Patients with no drug-related clinical adverse experience	881	(83.0)
Gastrointestinal Disorders	**57**	**(5.4)**
Diarrhea NOS	11	(1.0)
Flatulence	18	(1.7)
General Disorders and Administration Site Conditions	**16**	**(1.5)**
Musculoskeletal and Connective Tissue Disorders	**93**	**(8.8)**
Arthralgia	16	(1.5)
Muscle weakness NOS	12	(1.1)
Myalgia	57	(5.4)
Nervous System Disorders	**22**	**(2.1)**
Headache	13	(1.2)

NOS = Not otherwise specified.
Although a patient may have had two or more clinical adverse experiences in a body system, the patient is counted only once within a body system category total. The same patient may appear in different categories.
† Determined by the investigator to be possibly, probably, or definitely drug related.

One hundred twenty-five (11.8%) patients discontinued study drug due to a clinical adverse experience, 102 (9.6%) had drug-related adverse experiences, and 7 (0.7%) had serious adverse experiences. Table E-20 summarizes clinical adverse experiences that caused discontinuation from study drug due with ≥1% incidence in CUSTOM. Patients who discontinued study drug also had the opportunity to continue in the study until completion since the main objective of the study was to observe behavior of patients who chose to self-medicate rather than efficacy of lovastatin.

Table E-20

Number (%) of Patients Discontinued From Study Drug Due to Clinical Adverse Experience
by Body System (Incidence ≥1%)—CUSTOM Study

	Lovastatin 20 mg (N=1061)	
	n	**(%)**
Patients with one or more clinical adverse experience leading to discontinuation of study drug	**125**	**(11.8)**
Gastrointestinal Disorders	30	(2.8)
General Disorders and Administration Site Conditions	14	(1.3)
Musculoskeletal and Connective Tissue Disorders	67	(6.3)
Arthralgia	**13**	**(1.2)**
Myalgia	**39**	**(3.7)**
Nervous System Disorders	15	(1.4)
Although a patient may have had two or more clinical adverse experiences in a body system, the patient is counted only once within a category total. The same patient may appear in different categories.		

The Nonprescription Lovastatin Clinical Program was not designed to provide comparative safety data versus placebo. Since there was no control group in CUSTOM, formal comparisons with respect to adverse experience rates cannot be made; however, historical data from large placebo-controlled studies with prescription lovastatin may provide some perspective for the experience in CUSTOM.

As noted above, the incidence of muscle symptoms such as myalgia and muscle weakness in CUSTOM was ~11%. This rate is generally consistent with that reported in the 48-week EXCEL trial for these adverse experiences: 8.3% among the 1,642 participants on lovastatin 20 mg and 7.5% among the 1,663 participants on placebo [135]. There were no cases in EXCEL showing evidence of myopathy (defined as myalgias with a CK>10 x ULN) at the 20-mg dose. Similarly, data from the 5.2-year AFCAPS/TexCAPS trial indicate that the total number of patients reporting any musculoskeletal symptoms during the study was similar between treatment groups: 2,053 of 3,304 (62.1%) and 1,971 of 3,301 (59.7%) receiving lovastatin (20-40 mg/day) and placebo, respectively; p=0.563 [136]. Discontinuations due to myalgia were similar in both groups: 11 (0.3%) and 9 (0.3%) with lovastatin and placebo respectively; p=0.824. Rhabdomyolysis was rare, with only 1 case among lovastatin patients (unrelated to study treatment), and there were no cases of uncomplicated myopathy [136].

These data are useful only for making general comparisons since EXCEL and AFCAPS/TexCAPS were significantly longer trials than the 26-week CUSTOM study. In addition, the CUSTOM trial was an uncontrolled open-label study, where both patients and investigators were aware that active treatment was being provided. It is also important to recognize that at the time of the CUSTOM study, there was likely a heightened consumer awareness of muscle symptoms and adverse experiences based on the multiple warnings and icons in the label and other educational materials. The need to beware of unexplained muscle pain may have influenced some patients to be more likely to report such pain. Furthermore, musculoskeletal complaints are commonly seen among adults, with 280 physician visits per 1000 people in the United States designated as being specifically for musculoskeletal pain for the year 2000 [137].

In addition to monitoring of clinical adverse experiences, ALT tests were done at the first study site visit and at the end of the study. If ALT increased ≥3 x ULN at the end of the study, the investigator was to evaluate this occurrence as a laboratory adverse experience. Of the 1,061 patients who were included in the assessment of safety, 986 (92.9%) comprised the population of patients with a laboratory test postbaseline. Only 5 (0.51%) of the 986 patients had a laboratory adverse experience at the end of the study. One patient had an incidental finding of increased PSA, unrelated to study drug. The remaining 4 had elevated ALT measurements, which the investigators determined as drug related. However, only 3 of these patients had ALT >3 x ULN; the other patient had only slightly increased transaminases (1.5 x ULN).

In conclusion, no new safety issues were revealed in CUSTOM. Lovastatin was generally well-tolerated. The safety and tolerability profile demonstrated in this study is consistent with that shown in the larger, randomized, placebo-controlled EXCEL and AFCAPS trials.

6. Summary—Safety of Lovastatin

A large body of safety information has been collected on lovastatin. Postmarketing monitoring of the population exposed to lovastatin over the last 17 years is reflected in the adverse experiences reported in WAES. Both serious and nonserious adverse experiences reported are consistent with the known effects of the drug and typical underlying disease states. There are no new safety concerns. Serious adverse experiences are infrequent at the 20-mg dose of lovastatin. Additionally, the CUSTOM study has shown that lovastatin 20 mg is generally well tolerated when used by patients who have self-selected according to the proposed label.

The data reviewed in this Safety Summary indicate that lovastatin 20 mg can be safely marketed with appropriate labeling in the OTC environment for generally healthy individuals with ≥ 2 risk factors and a ≤ 20% risk of CHD over 10 years. These data suggest a very low incidence of medically significant adverse experiences (i.e., myopathy) when used according to the proposed warnings and directions. The label

informs consumers to avoid medications that may interact with lovastatin, and to stop taking lovastatin and see a physician if they develop unexplained muscle pain, tenderness, or weakness. Because of the large margin of safety and the low dose proposed for nonprescription availability, consumers who occasionally make errors are unlikely to experience an adverse event.

7. Conclusions—Safety of Lovastatin

- Long term, chronic use of lovastatin at prescription doses of 10 to 80 mg daily is well tolerated. In controlled clinical trials, the safety profile of lovastatin 20 mg daily is comparable to that of placebo. No new safety issues exist that have not been previously identified.
- Lovastatin 20 mg daily has an excellent safety profile when used for up to 6 months in the nonprescription setting and for greater than 5 years in the AFCAPS/TexCAPs postmarketing trial.
- There are no clinically meaningful differences in the safety profile of lovastatin 20 mg once daily with regard to gender, age, or race.
- Review of the experience with prescription doses of lovastatin (including doses higher than 20 mg once daily) demonstrates that lovastatin is generally safe in patients with hypertension, diabetes mellitus, renal disease, or thyroid disease. Use in individuals with active liver disease and excessive alcohol use is contraindicated, but evidence supports safety in OTC type populations if used without LFT monitoring or checking baseline LFTs.
- In a review of the reports on lovastatin during pregnancy, no prospective reports of congenital anomalies were identified for lovastatin, and no pattern of anomalies was identified among the retrospective reports. The rate of congenital anomalies in prospectively reported pregnancies is similar to the background rate. However, the number of prospectively reported cases with a known outcome that were available for analysis is small. In view of the limited benefits of this drug in premenopausal women, nonprescription lovastatin will be indicated only for women aged 55 or older and, like all OTC drugs, will be contraindicated during pregnancy.
- Although myopathy and rhabdomyolysis in particular, may be considered the adverse experience of primary interest for the HMG-CoA reductase inhibitors, both clinical study experience and market-use experience indicate that these occurrences are rare. The risk of lovastatin-associated myopathy appears to increase with increasing dose of lovastatin. Myopathy is a symptomatic condition that can be recognized by patients and usually resolves after drug discontinuation. Therefore, clinical consequences can be limited by a warning on the label to stop taking lovastatin and consult a physician if unexplained muscle pain, tenderness, or weakness occurs.

- Concomitant treatment with strong CYP3A4 inhibitors (cyclosporine, clarithromycin, itraconazole, ketoconazole, nefazodone, erythromycin, HIV protease inhibitors, and grapefruit juice >1 quart/day) may increase plasma HMG-CoA inhibitory activity levels, and therefore may increase the individual's risk of myopathy. Concomitant use of other lipid-lowering agents may also increase the risk of myopathy, especially the use of gemfibrozil and to a lesser extent other fibrates or lipid lowering doses of niacin. However, the associated risk of myopathy is very low with the 20-mg dose of lovastatin, and would be expected to remain low even with concomitant use of a strong CYP3A4 inhibitor. Concomitant use of any drugs with lovastatin is contraindicated on the nonprescription label, without first consulting a health care professional.
- Occasional asymptomatic elevations of serum transaminase are dose-dependent, and have not generally been noted to progress to clinical liver disease; the incidence of confirmed ALT elevations >3 x ULN is similar with lovastatin 20 mg daily and placebo. Clinically apparent liver disease (hepatitis, hepatic failure) associated with lovastatin use at any dose is rare. Patients with asymptomatic, undiagnosed liver disease do not appear to be at an increased risk of developing worsening of the liver disease. Therefore, routine baseline testing and periodic monitoring of liver function tests (LFTs) would not be of value in users of lovastatin 20 mg once daily.
- Given the large margin of safety, lovastatin 20 mg has a safety profile appropriate for use in the nonprescription setting.

F. MEVACOR OTC SELF-MANAGEMENT SYSTEM AND POST-LAUNCH MARKET MONITORING PLANS

1. Introduction

J&J◦Merck has developed a comprehensive approach to encourage proper consumer behavior in the marketplace through the development of a unique MEVACOR™ OTC "Self-Management System" that includes multiple tools. The components of the SMS were fully developed and tested in the CUSTOM study. Details are provided in Section G. Consumer Behavior and actual samples of the key components of the SMS are in Appendix I.

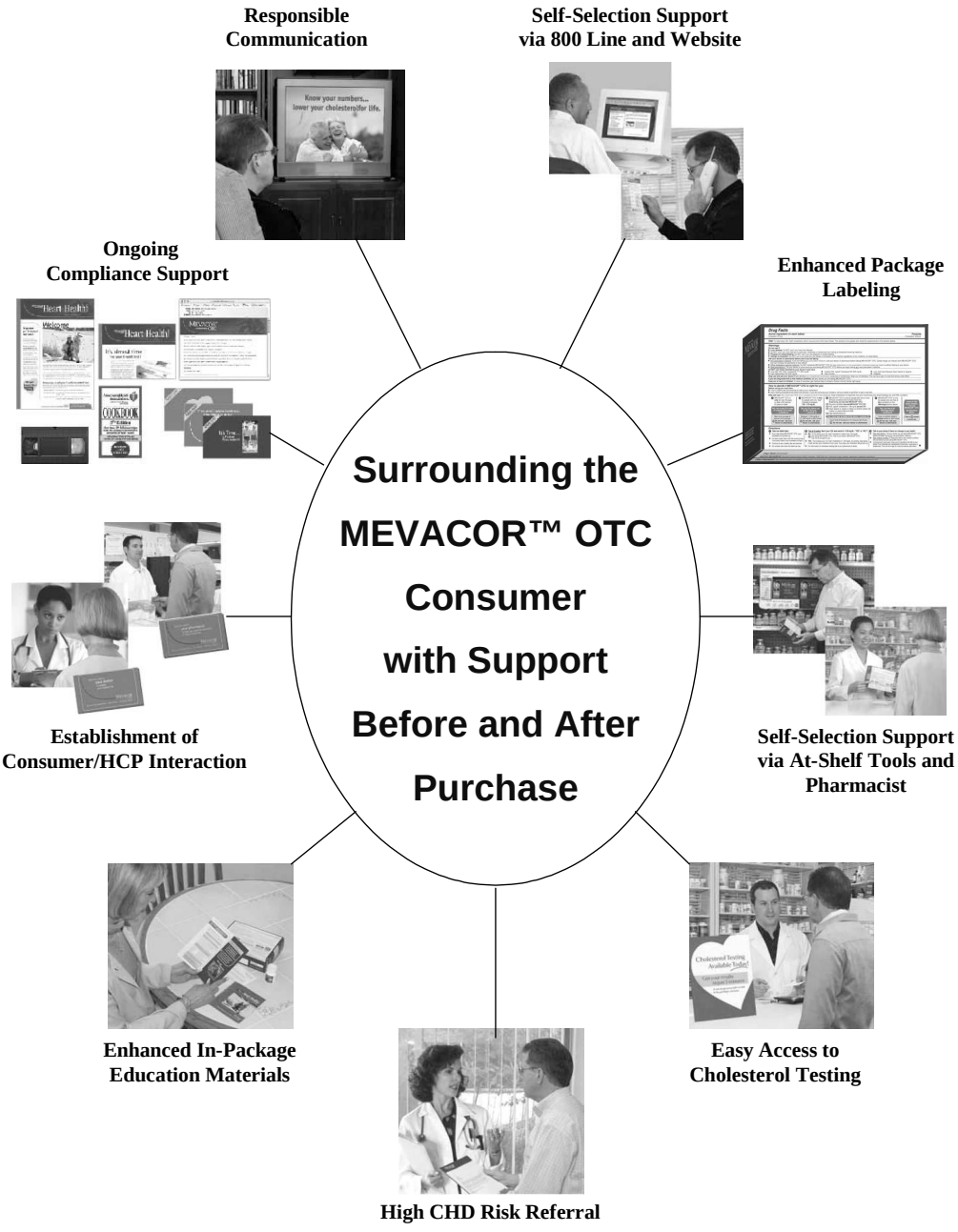
Individual consumers have unique learning styles. Therefore, the goal of the System is to surround consumers with numerous usage management tools recognizing that the consumer will gravitate towards the materials consistent with their own style of learning.

The System emphasizes a "collaborative care" approach and is designed to support self-management while encouraging proper interaction with healthcare professionals when appropriate.

The MEVACOR™ OTC Self Management System represents an advance beyond currently marketed OTC products. It is a comprehensive consumer support system designed to meet the following objectives:

- Responsibly educate consumers regarding cholesterol, diet, exercise, and overall heart health as part of the appropriate use of MEVACOR™ OTC
- Direct consumers with higher risk of CHD to physicians for more comprehensive medical care
- Assist the consumer with initial self-selection via a toll-free hotline and website
- Assist the consumer with initial self-selection and ongoing use at the retail point of purchase
- Direct appropriate consumer behavior through enhanced labeling and educational materials inside the package
- Facilitate easy consumer access to cholesterol testing
- Encourage long-term compliance and persistence with therapy
- Encourage consumer interaction with healthcare professionals when appropriate
- Provide ongoing cholesterol management support through a regular, scheduled series of communications (i.e., newsletters, e-mails)
- Educate healthcare professionals regarding the use of MEVACOR™ OTC

Because consumer research has indicated that not every consumer will choose to take advantage of every tool provided, the System has been designed to surround consumers with consistent messages about the appropriate use of MEVACOR™ OTC. The expected result of this comprehensive System design is that the vast majority of consumers will utilize some of the tools, and that all consumers will receive the same key support messages.


Responsible Communication
Know your numbers... lower your cholesterol for life.
Self-Selection Support via 800 Line and Website
Ongoing Compliance Support
Heart Health!
COOKBOOK
Enhanced Package Labeling
Drug Facts
Surrounding the MEVACOR™ OTC Consumer with Support Before and After Purchase
Establishment of Consumer/HCP Interaction
Self-Selection Support via At-Shelf Tools and Pharmacist
Enhanced In-Package Education Materials
High CHD Risk Referral
Cholesterol Testing Available Today!
Easy Access to Cholesterol Testing

2. Self-Management System Tools and Marketplace Implementation

2.1. Usage Management Tools Included in Self -Management System

J&J◦Merck has developed a system of tools designed to achieve the objectives stated above. The Usage Management tools included in the Self-Management System are described below.

2.1.1 Limited Marketplace Distribution and Enhanced Retail Support Tools

J&J◦Merck will limit the distribution of MEVACOR™ OTC and provide enhanced in-store consumer assistance with self-selection and ongoing use support. Included are the following:

- Product sale restricted to retail stores with pharmacies so there is convenient access to the pharmacist should the consumer have questions (approximately 50,000 stores with pharmacies versus the approximately 250,000 stores currently selling other OTC products)
- Training of in-store pharmacists and appropriate pharmacy and retail support staff on MEVACOR™ OTC and appropriate consumer use of the product
- In-store consumer educational materials/self-selection devices (e.g., brochures, on-shelf devices) that also refer to the availability of the Pre-Purchase Consumer Assistance Program
- Joint retail partnerships to ensure consumers have the option to enroll in the Post-Purchase Consumer Assistance Program
- The MEVACOR OTC system can be one of the first OTC products to be a part of the "Pharmacy Care" category currently being proposed by the American Pharmacist Association (APhA).
- Sponsorship of periodic cholesterol screening events at retail pharmacies

In Retail Stores with Pharmacies Only

Shelf Unit with Self-Selection Tool and Educational Brochure

Pre-Purchase Consumer Assistance

Cholesterol Screening at Retail

2.1.2 Healthcare Professional Collaborative Care Messages

Although healthcare professional consultation is not a requirement for product use, the MEVACOR™ OTC Self-Management System strongly encourages consumer interaction with healthcare professionals when appropriate. Consumer communication, label, and internal package materials will instruct the consumer to talk with their doctor or pharmacist if they have any questions about whether or not MEVACOR™ OTC is right for them.

For those who decide to use the product, doctor and pharmacist notification cards will be included in the package. In addition, through the Pre-Purchase Consumer Assistance Program, consumers will have the ability to access a toll-free hotline and website with an option for a live discussion with a trained product specialist who is a healthcare professional. J&J◦Merck will also provide:

- Targeted communications to doctors and healthcare professionals concerning product benefit and proper use
- Partnerships with key third party healthcare organizations (e.g., American Heart Association, American Dietetic Association, American Pharmacist Association, National Consumers League) to coordinate messages and disseminate materials to educate consumers on cholesterol management

Pharmacist and Physician Notification Cards Included in Packaging

Pharmacist and Physician Educational Kits

2.1.3 High CHD Risk Consumer Identification and Referral Service

As a result of MEVACOR™ OTC availability, data suggest that most consumers will contact J&J◦Merck via the consult with their doctor and/or pharmacist or the toll-free hotline. Some will have a higher CHD risk than the OTC label target population and will not be appropriate candidates for the product. For those who are at higher CHD risk, J&J◦Merck will recommend to these people that they see their physician for appropriate treatment via various methods including package labeling, website and personal communication should they choose to contact us.

The High CHD Risk Referral Service will be provided in both the Pre- and Post-Purchase Assistance Programs. In addition, we will provide education to healthcare professionals on how to identify higher CHD risk consumers.

Encourage Testing

Assistance in Interpreting Test Results

Encourage Physician Interaction for Higher-Risk Individuals

2.1.4 Consumer Communication Plan (Advertising, PR, etc.)

J&J◦Merck is committed to promoting MEVACOR™ OTC in an ethical and responsible manner targeting consumers who are appropriate for the OTC product. Education and awareness messages will emphasize:

- Benefit of reducing cholesterol to lower the risk of heart disease
- Importance of "knowing your cholesterol numbers"
- Appropriate self-selection and de-selection criteria for MEVACOR™ OTC Consultation of healthcare professionals when appropriate (e.g., in-store pharmacists)

The above messages will be communicated through vehicles such as advertising (television, radio, print), public relations, education of healthcare professionals, and consumer education materials.

Responsible Communication

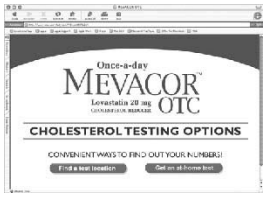
2.1.5 Pre-Purchase Consumer Assistance Program

Realizing the importance of proper self-selection, J&J◦Merck has developed a Pre-Purchase Consumer Assistance Program to assist consumers with the self-selection process if needed. Using a toll-free hotline, website or interactive retail tools, consumers will be taken through selection criteria in a simple, easy to understand, step-by-step manner. In-market advertising will encourage consumers to take advantage of this selection assistance prior to product purchase.

2.1.6 Cholesterol Testing Referral Service

With the availability of MEVACOR™ OTC, access to cholesterol testing will be important to help the consumer determine if he or she is an appropriate candidate to use the product (pre-treatment testing), and to monitor levels at regular intervals to ensure an appropriate treatment goal is reached and maintained (follow-up testing). Therefore the MEVACOR™ OTC Self Management System will include a program on how consumers can get an initial test and obtain pre-treatment cholesterol test results. This service will also encourage follow-up testing and provide an easy to understand interpretation of cholesterol test results.

In addition to providing assistance with cholesterol testing, J&J◦Merck commits to sponsor periodic convenient screening events (e.g., at retail pharmacies), as well as establishing partnerships with testing and device companies to communicate clear test result interpretations.



Online Cholesterol Testing Referral Service

Cholesterol Testing Event

2.1.7 Informative Packaging and Self-Management Materials

An informative package label will assist consumers with the initial self-selection decision by allowing them to assess their own eligibility. Internal package materials will include incentives to contact a toll-free hotline or website to enroll in the Post-Purchase Consumer Assistance Program. This point of contact will also be used to reinforce key label information prior to, or during product use. In addition, the following internal package materials will further encourage appropriate consumer behavior regarding comprehension of self-selection, treatment to goal, and de-selection messages:

- "Quick-Start Guide" outlining the self-selection criteria, treatment to goal, and ongoing monitoring
- Educational brochure providing in-depth information on long-term cholesterol management, including diet, exercise, and smoking cessation

- Notification cards consumers can share with their doctor and pharmacist informing them that they are using MEVACOR™ OTC
- Information and an incentive to obtain a cholesterol test
- Assistance with interpretation of cholesterol test results (via toll-free hotline, website, in-package materials, and Post-Purchase Consumer Assistance Program communication, see below for details)
- Mail-in offer to receive a free video (or DVD) reinforcing the importance of proper use and the role of long-term lifestyle management
- Incentives to enroll in the Post-Purchase Consumer Assistance Program
- Informative package insert in Question and Answer format

2.1.8 Post-Purchase Consumer Assistance Program

By calling the toll-free hotline, visiting the website, or returning a business reply card, consumers may enroll in the MEVACOR™ OTC Post-Purchase Consumer Assistance Program. The multi-faceted Post-Purchase Program will provide communication to the consumer via newsletters, mail, e-mail and telephone to encourage compliance, persistence and behavior modification. Included in the Post-Purchase Program:

- Link to High CHD Risk Doctor Referral Program
- Full product refund for consumers who learn they should not continue taking MEVACOR™ OTC
- Link to MEVACOR™ OTC Cholesterol Testing Referral Service
- Scheduled series of communications (i.e., newsletters, postcards)

Post-Purchase Compliance Education and Support

2.2 Marketplace Execution

J&J◦Merck is committed to working with leading organizations in health advocacy, cholesterol testing, and the retail trade to ensure the complete and effective implementation of the Self Management System.

Regular briefings on the progress of the MEVACOR™ OTC program have been provided to key organizations and, following approval, J&J◦Merck will be collaborating with them to provide consistent consumer messaging about lipid control and heart disease, optimal consumer access to cholesterol testing in conjunction with the Cholesterol Testing Referral Service portion of the Self Management System, and effective retail implementation of the in-store elements of the Self Management System.

J&J◦Merck has committed, as terms of NDA approval, to ensure that these same programs will be implemented in the marketplace along with appropriate HCP training. All printed materials are considered to be regulatory labeling and cannot be eliminated or changed without FDA approval.

G. CONSUMER BEHAVIOR

1. Introduction

The original New Drug Application (NDA) for nonprescription lovastatin 10 mg was submitted to the United States Food and Drug Administration (FDA) on 10-Dec-1999. Important goals of the lovastatin OTC (over-the-counter) development program were to demonstrate that consumers will self-select to use the product when appropriate, reject use of the product when inappropriate, and persist with treatment over time to achieve potential health benefits. Data supporting these goals were provided from 3 Actual Use studies: Protocols 076, 079, and 081. These data were reviewed by the Non-Prescription Drugs and Endocrine and Metabolic Drugs Advisory Committees in July 2000.

Since 2000, there have been numerous communications between the FDA and J&J◦Merck aimed at obtaining specific guidance and recommendations on continued development of nonprescription lovastatin. Although the proposed OTC dose has shifted to 20 mg, the consumer behavior data from the original NDA remain valid and provide support for nonprescription availability of lovastatin, and where appropriate, these data will be re-summarized in this section of the Background Information. However, as a result of input from FDA, the OTC treatment paradigm, product labeling, and consumer support materials have significantly evolved from the original NDA, and additional consumer behavior data have been generated to support approval of this application.

1.1 Evolution of Treatment Paradigm and Labeling

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines released in May-2001 recommended consideration of pharmacologic therapy for all individuals with multiple coronary heart disease (CHD) risk factors (2 or more), and a 10-year hard CHD (myocardial infarction or coronary death) risk of ≤20%, whose low density lipoprotein cholesterol (LDL-C) remained above the goal of <130 mg/dL after a trial of therapeutic lifestyle changes [22]. In an effort to be consistent with the cholesterol management-to-goal guidelines established by ATP III, J&J◦Merck developed, with guidance from both the FDA and independent experts (Board of Advisors for MEVACOR™ OTC), a revised treatment and labeling paradigm which is embodied in a multifaceted program termed the MEVACOR™ OTC Self-Management System (MOTC-SMS). The MOTC-SMS focuses on the primary prevention of CHD in a subset of individuals with multiple (2 or more) risk factors and a 10-year CHD risk ≤20% that approximate the intermediate risk group. In order for this population to be able to attain the ATP III-designated LDL-C target goal of <130 mg/dL, the daily dose proposed for nonprescription lovastatin was increased from the 10 mg proposed in 2000 to 20 mg. The MOTC-SMS which is described and evaluated in this summary consists of the same materials tested in the clinical Actual Use Study 084 titled: A Consumer Use Study of OTC MEVACOR™ (CUSTOM).

The essence of the MEVACOR™ OTC Self-Management System is the product carton label. The goal in developing the MEVACOR™ OTC product label was to be consistent with ATP III, and for the label to be readily understood and followed by the majority of consumers. The proposed MEVACOR™ OTC carton label specifies that the product may be used, following a trial of diet and exercise, by individuals with LDL-C between 130 and 170 mg/dL, age (≥45 years for men and ≥55 years for women), and one additional risk factor (smoking, family history, hypertension, or HDL <40 mg/dL). It was anticipated that 80% of consumers meeting these criteria would be able to reach their ATP III defined goal of LDL-C <130 mg/dL with the 20-mg dose of lovastatin. People with known current liver disease, history of muscle pain, weakness or tenderness while taking a cholesterol-lowering agent, pregnancy or breast-feeding, and allergies to lovastatin are directed by the label not to take the product. Consumers are directed by the label to seek physician or healthcare professional consultation for a number of situations. Table G-1 provides a schematic of the key elements of the carton label.

Table G-1

Key Elements of the Proposed MEVACOR™ OTC Carton Label

Use: To help lower LDL "bad" cholesterol, which may prevent a first heart attack.

Warnings

Do not use if:

- you have **liver disease**
- you have had any muscle pain, weakness, or tenderness from taking a cholesterol-lowering medicine
- you are **pregnant or breast-feeding**
- you know you are **allergic to lovastatin** or the inactive ingredients in this medicine

Ask your doctor or pharmacist before use if you are taking:

- any prescription medicine
- other cholesterol-lowering medicine (prescription or nonprescription)
- before starting new prescriptions: tell your doctor you are taking MEVACOR™ OTC

Do NOT use unless directed by your doctor if you have:

- very high LDL "bad" cholesterol 171 to 400 mg/dL
- high triglycerides 200 to 900 mg/dL
- healthy HDL "good" cholesterol 60 to 200 mg/dL
- had a stroke
- ever had heart disease (heart attack or angina)
- diabetes

Stop use and ask your doctor if you develop any unexplained muscle pain, weakness or tenderness.

If you are diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.

How to decide if MEVACOR™ OTC is right for you

Before using you must have:

- Tried a healthy diet and exercise to reduce your cholesterol.
- Had a fasting cholesterol test within the last year.

Who can use: MEVACOR™ OTC is only for:

1. men 45 years or older **AND** women 55 years or older
2. people with LDL "bad" cholesterol between **130 to 170 mg/dL**
3. people with one or more of these conditions that increase heart disease risk:
   - You are a smoker
   - HDL "good" cholesterol 1 to 39 mg/dL **(too low)**
   - Heart attack or angina in father or brother before 55; mother or sister before 65 **OR**
   - High blood pressure

Directions

1. **Take one tablet daily:**
   - Continue to eat a healthy diet and exercise.
2. **Test at 6 weeks: See if your LDL test result is below 129 mg/dL: "Yes" or "No"?**
   - NO – If at 6 weeks your LDL "bad" cholesterol is higher than 129 mg/dL, stop taking MEVACOR™ OTC. Talk to your doctor. MEVACOR™ OTC may not be enough for you.
   - YES – If at 6 weeks your LDL "bad" cholesterol is below 129 mg/dL, it's working, keep taking it daily and test your cholesterol once a year. If you stop, your cholesterol will go back up.
3. **Talk to your doctor if there is a change in your health:**
   - New prescriptions: Tell your doctor you are taking MEVACOR™ OTC before you begin taking any new prescription medicine.
   - New medical condition: If diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.
   - **Unexplained muscle pain: Stop use immediately** and talk to your doctor if you develop any unexplained muscle pain, weakness, or tenderness. This can be a sign of a rare but serious side effect.

The MEVACOR™ OTC Self Management System embodies an interactive collaborative care approach designed to appropriately empower consumers without leaving them unsupported. In addition to the product carton label, the MOTC-SMS includes shelf display materials, product carton and bottle, package insert, Quick Start Guide, educational brochure, video, product website, toll-free call center, and cholesterol testing referral service (samples of the printed materials are in Appendix I). A Consumer Assistance Program (called the Heart Health Program), which is a component of the MOTC-SMS, provides compliance and appropriate de-selection support for consumers choosing to enroll. The Consumer Assistance Program consists of postcard reminders, e-mails, and newsletters. Consumers can enroll through the toll free phone number, the website, or with the pharmacist at the point of purchase. These tools are provided to maximize communication effectiveness and guide consumer behavior in using the product correctly when it is right for them, or in directing them to consult a physician for more comprehensive care.

1.2 Evaluation of Consumer Behavior

In order for lovastatin 20 mg to be considered suitable for nonprescription status, the MEVACOR™ OTC Self-Management System should meet the following criteria regarding consumer behavior:

- Consumers should demonstrate sufficient comprehension of the text on the product label to allow appropriate decision-making regarding product use
- Consumers should self-select to use the product when appropriate according to the labeling, and not use the product when inappropriate
- Consumers should follow the directives and make appropriate decisions about continued use of the product and consultation with healthcare professionals
- Consumers should persist with treatment over time to achieve potential health benefits

With advice and guidance from the FDA, studies were designed and conducted to evaluate consumer comprehension and actual behavior regarding the new labeling and support materials. The data from these studies demonstrate that the MEVACOR™ OTC Self-Management System meets each of the above criteria.

2. Label Comprehension—Pivotal Label Comprehension Study

The primary objective of the Pivotal Label Comprehension Study (Pivotal LCS) was to determine the percent of respondents who can demonstrate that they understand the MEVACOR™ OTC package label by being able to correctly answer questions about specific elements of the label as well as apply their understanding to “scenarios” that combine multiple elements. Secondary objectives focused on self-selection as well as the evaluation of results among low literacy and non-Caucasian subgroups. This was a one-cell study, with 696 representative respondents chosen randomly in 25 geographically

and demographically dispersed shopping malls, as well as an additional 92 respondents chosen to augment the low literacy subgroup (111) in the representative sample. Participants were screened to be cholesterol-concerned and neutral to positive on the general concept of an OTC cholesterol-lowering product called MEVACOR™ OTC. They reviewed the same package label used in the CUSTOM Study, and then answered comprehension and self-selection questions.

In general, respondents in the MEVACOR™ OTC Pivotal LCS demonstrated that they understood the key messages being communicated. Respondents showed they were able to use the label effectively to choose appropriate next steps for a wide variety of hypothetical situations presented to them via scenario testing. There were few instances when respondents gave a "can use" response for a hypothetical person who should have talked to a doctor first or not used the product. Results were particularly strong for scenarios regarding safety concerns (correct + acceptable scores nearly all > 90%).

Although self-selection was a secondary goal of the study, results were also satisfactory, as 90% of respondents made a correct or acceptable self-selection decision. A closer examination of subgroups, such as those respondents who were in a demographic or medical group excluded by the label, showed similar satisfactory self-selection scores. It should be noted that self-selection data within the context of a label comprehension study conducted in mall sites should be used for general guidance and not considered as definitive self-choice data. Because there is no opportunity for respondents to make an actual purchase, the task of deciding whether they are appropriate to use a product during a study of this type is difficult for many people. The primary source for self-selection data is the CUSTOM Actual Use study (Protocol 084).

Finally, on most key measures, the low literacy and non-Caucasian subgroups did not score significantly lower than their respective comparison groups. This was particularly true for important safety precautions and warnings, as well as for self-selection. See Appendix G for details of results from the Pivotal LCS.

3. Consumer Behavior Results From the Actual Use Studies

Table G-2 provides summary descriptions of the Actual Use studies that comprise the clinical development program for nonprescription lovastatin, and the use study data summarized in this Background Information are identified in Table G-3. The primary focus of this Consumer Behavior Summary is on data from the CUSTOM Study since it represents the current treatment paradigm, product labeling, and support materials. However, as stated earlier, when relevant data are available from the nonprescription lovastatin 10-mg studies, these data will be re-summarized in the appropriate sections. Although this section of the Background Information is devoted to summarizing consumer behavior, a brief summary of lovastatin 20 mg efficacy and safety in CUSTOM is included as part of the presentation of results from CUSTOM. More details of efficacy and safety results from CUSTOM are presented in Sections C and E, respectively.

Table G-2

All Open-Label Use Studies for Nonprescription Lovastatin

Protocol Number	Short Study Name/Study Description/Setting	Design	Treatment Duration	Took Study Drug (N)
Lovastatin 20 mg (Amended 2004 NDA Resubmission)				
084	**CUSTOM Study**: Consumer behavior study of the MEVACOR™ OTC Self-Management System in a storefront setting	Open label Non-comparative All-comers (minimal exclusions) Purchase required for drug and cholesterol test	6 months	1061
Lovastatin 10 mg (Original 1999 NDA Submission)				
076	**Pharmacy Study**: Participant self-selection in the treatment of elevated cholesterol in a pharmacy setting.	Open label Non-comparative All-comers for purchase intent Screened by Pharmacist for drug dispensing	24 weeks with two 6-month extensions (total: 18 months)	722
079	**Restricted Access Study**: Restricted access study in the treatment of elevated cholesterol in a storefront setting.	Open label Non-comparative Pre-screened by telephone product specialist	8 weeks	460
081	**Red Arrow Study**: Participant self-selection in the treatment of elevated cholesterol in a storefront setting.	Open label Non-comparative All-comers Purchase required for drug	4 weeks	1144

Table G-3

Use Study Consumer Behavior Data Summarized
in This Background Information Document

Use Study	OTC Drug Distribution Paradigm	Use Decisions		Cholesterol Knowledge[§]	Compliance/ Persistence
		Self-Selection	Continued Use[‡]		
Lovastatin 20 mg (Amended NDA Resubmission)					
CUSTOM Study (Protocol 084)	Open shelf	✓	✓	✓	✓
Lovastatin 10 mg (Original NDA Submission)					
Pharmacy Study (Protocol 076)	Open shelf			✓	✓
Restricted Access Study (Protocol 079)	Restricted access[†]			✓	
Red Arrow Study (Protocol 081)	Open shelf	✓			

[†] Participants had no access to treatment unless found potentially eligible by a product specialist at a toll-free telephone screening service.

[‡] Continued use decisions (de-selection) with regard to label directives included treatment to target goal (LDL-C <130 mg/dL), new prescription medications, and emergent medical conditions including unexplained muscle pain.

[§] Participant's measured cholesterol values taken at baseline were compared to the values reported on the questionnaire.

CUSTOM Study Design

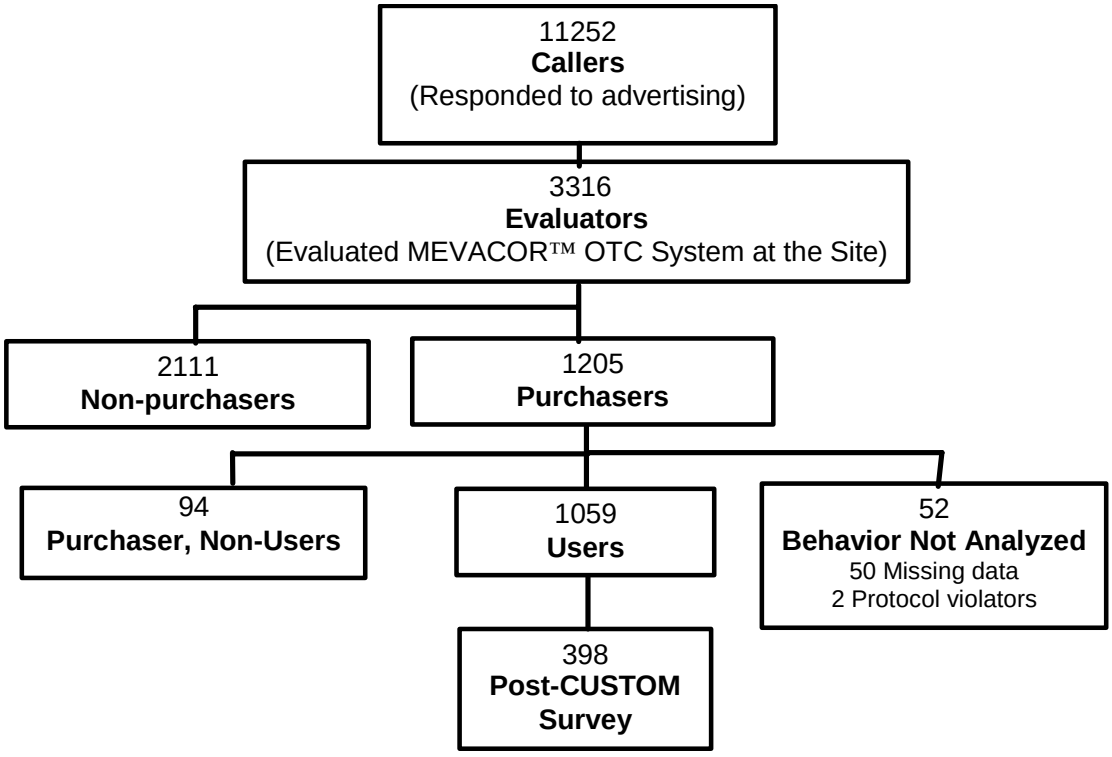
Because most of the consumer behavior data presented in this summary is from the CUSTOM Study (Protocol 084), it is important to understand the study design. CUSTOM was an open-label, uncontrolled, "all-comers," consumer behavior observation study conducted in 14 geographically dispersed strip mall sites (shopping centers) throughout the United States. Participants were recruited by mass media advertising to the storefront study sites, which included a study drug purchase area designed to simulate a retail pharmacy environment. All participants had the opportunity to read the proposed outer carton label or interact with the in-store materials (e.g., shelf display), and indicate if they were interested in purchasing a carton of 45 tablets for $15 (i.e., yes, no, or need more information before purchasing). Participants were allowed to purchase a total of 4 cartons during the study either as single or multiple carton purchases. Initial payment was made prior to obtaining informed consent. If participants needed cholesterol values and asked about cholesterol testing at the study site, they were directed to an area of the site where they could decide to purchase a test for $10.

CUSTOM was carefully designed not to interfere with or influence participant self-selection or de-selection decisions. Since J&J◦Merck is proposing that MEVACOR™ OTC will only be sold in retail locations that have pharmacy personnel on-site during normal business hours to answer questions about the product, the study nurse-investigators functioned as pharmacists, and could answer questions initiated by the participant relating to the study or study drug. As planned for the market place, if a participant requested assistance in deciding whether or not to purchase MEVACOR™ OTC, the nurse-investigator, functioning as the pharmacist, could help the participant through the standardized self-selection eligibility assessment. Prior to making a purchase decision, participants were allowed to leave the study site (one time only) to consult a personal physician, obtain a new cholesterol test, fast, or obtain test values on file at their physician's office, and return once the information was obtained to make a repeat purchase decision. Only the initial visit to the study site and the final visit (6 months) were scheduled. Purchasers were informed that they could return to the storefront at any time during the 26-week period to purchase additional medication or a cholesterol test. After completion of the study, subsets of participants who used study drug and agreed to be contacted were asked additional questions about their experience in the clinical study and their opinions about the product and related materials (Post-CUSTOM Clarification Questions, Post-CUSTOM Survey).

Figure G-1 is a diagram of participant flow through the CUSTOM study. The results presented in the following sections primarily focus on Evaluators, Non-Purchasers, and Users. Of the 3,346 participants who visited the study sites, 3,316 evaluated the Self-Management System for potential product purchase (Evaluators), 2,111 did not buy MEVACOR™ OTC (Non-Purchasers). A total of 1,061 participants took at least one dose of MEVACOR™ OTC (Users), but 2 were protocol violators, leaving 1,059 Users for analysis of initial use and ongoing use behavior.

Figure G-1

CUSTOM: Participant Flow Through Study



3.1 Demographics of Clinical Study Populations

3.1.1 Advertising Campaigns

Of the 4 Actual Use studies, Protocol 084 (CUSTOM) incorporated the most comprehensive ethnic recruitment strategy. Prior to development of the advertising strategy, focus group sessions were held with Black and Hispanic individuals to determine the optimal messages and media for successfully recruiting an ethnically diverse population. Ethnic media were evaluated to determine the most effective television and radio stations, programming, and publications to reach Black and Hispanic populations. All of the initiatives noted above were utilized to ensure recruitment of a diverse consumer population with an ethnic mix that was representative of the United States population.

3.1.2 Demographic Characteristics

The consumers that responded to the study recruitment advertising represent a group that may be interested in using a nonprescription cholesterol-lowering product in the marketplace. Some common demographic characteristics of these consumers are summarized in Table G-4.

The study advertisements were effective in recruiting middle-aged individuals. The population responding to the advertisements included a somewhat larger proportion of males than females. Although racial origins were mostly White, the results from CUSTOM (Protocol 084) demonstrate that a well-executed ethnic advertising strategy can attract a population with an ethnic mix representative of the United States population. Because the study participants were recruited in extensive and diverse media markets, it is anticipated that the demographic composition of interested consumers in the marketplace for this product will be similar in character to the demographic composition observed in these 4 use trials.

Table G-4

Participants Responding to Study Advertising—Demographic Characteristics

	CUSTOM Study (Protocol 084)	Pharmacy Study (Protocol 076)	Restricted Access Study (Protocol 079)	Red Arrow Study (Protocol 081)
Number of participants visiting study sites (Protocols 084, 076, 081) or screened by product specialist at toll-free number (Protocol 079)	3346	6095	4878	2416
Males	1962	3416	2818	1646
Females	1384	2649	2040	671
Gender data missing	0	30	20	99
Mean age (years)				
Enrolled/qualified	56.5[†]	60.0	57.7	55.9
Nonenrolled/nonqualified	51.7[†]	59.9	57.8	56.3
Racial origin	N (%)	N (%)	N (%)	N (%)
White	2393 (71.5)	5553 (91.1)[‡]	1129 (87.9)[§]	1949 (80.7)[‖]
Black	632 (18.9)	181 (3.0)[‡]	63 (4.9)[§]	155 (6.4)[‖]
Asian	68 (2.0)	47 (0.8)[‡]	39 (3.0)[§]	58 (2.4)[‖]
Hispanic	171 (5.1)	134 (2.2)[‡]	48 (3.7)[§]	68 (2.8)[‖]
Other/unknown	82 (2.4)	180 (3.0)[‡]	3599[§]	186 (7.7)[‖]

[†] For this table, enrolled/qualified in CUSTOM is defined as Users (N=1061), and Nonenrolled/nonqualified is defined as Non-Purchasers (N=2111).

[‡] Race information collected on participants at pharmacy sites for participants willing to give an answer (no difference noted in race distribution between all participants and those who were eligible).

[§] Race information not collected on telephone-screened participants but on all those visiting study sites and willing to give an answer. Percentages were based on the number of participants visiting site and having a known race (N=1285).

[‖] Race information collected on all participants with medical history forms available.

3.2 Cholesterol Knowledge and Accuracy of Self-Reported Values

3.2.1 CUSTOM Study (Protocol 084)

The recruitment advertising for CUSTOM informed consumers that, in order to participate, it was important for them to know their 4 cholesterol numbers (Total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides). Knowledge of LDL-C, HDL-C, and triglyceride values (but not Total-C) was necessary for participants to appropriately determine whether MEVACOR™ OTC was right for them without first consulting a physician. As previously noted, before deciding to purchase and use the product, participants had the option to purchase a cholesterol test at the study site, or to leave the site to obtain a cholesterol test or retrieve cholesterol numbers from a previous test. This was allowed in order to simulate the marketplace, where consumers could leave the store and return later to make a purchase decision. Participants who evaluated the product and associated materials (Evaluators) were asked for the results (exact values) from the cholesterol test that they used to make their initial decision to purchase or not purchase MEVACOR™ OTC. The responses provided by the Evaluators were used to assess knowledge of their exact cholesterol values at the time of the initial purchase/use decision. In addition, a mandatory cholesterol test was performed on all participants who decided to buy the product (Purchasers). The results of this test were compared with those reported by the participant to evaluate the accuracy of the self-reported values, but were not shared with participants who did not purchase a test. This section summarizes the results from CUSTOM regarding knowledge of cholesterol values as well as the accuracy of the self-reported values.

Cholesterol Knowledge

Self-reported lipid values were collected from Evaluators as part of the Eligibility Assessment questionnaire. Individuals who did not know their exact LDL-C, HDL-C and triglyceride values were considered to be ineligible for MEVACOR™ OTC, unless they consulted with a physician before initial use (as directed by the carton label). In that case, their subsequent use of MEVACOR™ OTC was considered to be appropriate. Table G-5 displays the numbers of Evaluators, Non-Purchasers, and Users (those who took at least 1 dose of study drug) who knew their lipid values at the time of the initial purchase decision. Because not every individual answered every question on the eligibility assessment, the numbers represented by denominator “M” on the table are variable depending on the number of responses received. The table also lists Users who did not know a particular lipid value but consulted with a physician prior to initial use.

A substantial proportion of participants in CUSTOM knew their lipid values at the time of the initial product purchase decision. Evaluators were slightly more likely to know their HDL-C and triglyceride values than their LDL-C value. In addition, Users were more likely to know their lipid values (LDL-C, HDL-C, and triglycerides) than Non-Purchasers, suggesting that some Evaluators may have decided not to purchase and use

MEVACOR™ OTC at least in part because they did not know their lipid values. Importantly, Table G-5 also shows that nearly half of the Users who did not know a specific lipid value talked to a physician before starting to use MEVACOR™ OTC. In fact, only 188 Users did not know all three lipid values and used the product without first consulting with a physician.

Thus, the data show that the majority of participants who evaluated MEVACOR™ OTC for potential purchase knew their exact LDL-C, HDL-C, and triglyceride values, and those who did not know their numbers were more likely not to purchase, or would consult with a physician prior to beginning product use. A relatively small proportion of Evaluators (188 of 3,316, 5.7%) purchased and used MOTC without knowing all their exact lipid values and without first consulting with a physician.

Table G-5

CUSTOM – Knowledge of Lipid Values Among Evaluators, Non-Purchasers, and Users

	Evaluators (N=3316)		Non-Purchasers (N=2111)		Users (N=1061)	
Lipid Knowledge†	n/ M‡	%	n/M	%	n/M	%
Knew LDL-C value	1835/2913	63	1051/1783	59	716/1034	69
Did not know LDL-C but talked to physician					144/1034	14
Knew HDL-C value	1947/2939	66	1120/1799	62	758/1044	73
Did not know HDL-C but talked to physician					134/1044	13
Knew triglyceride value	1968/2935	67	1136/1795	63	762/1044	73
Did not know triglycerides but talked to physician					129/1044	12

† Participants can be counted in more than one lipid group
‡ M represents the number of Evaluators, Non-Purchasers, Users who provided a response on the eligibility assessment.

Accuracy of Self-Reported Cholesterol Values

As previously noted, the design of this study included the collection of each participant's self-reported lipid values prior to purchase of study drug as well as the determination of a measured baseline lipid profile. This permitted the assessment of agreement between self-reported and measured lipid values.

For LDL-C, 667 of the User population had both a known self-reported LDL-C value and a non-missing measured LDL-C from the fingerstick evaluation performed at the study site on a desktop analyzer. The results from each were categorized using 3 categories: <130 mg/dL, 130 to 170 mg/dL, and >170 mg/dL. A total of 505 (75.7%) of the 667 had a self-reported LDL-C that agreed with the measured LDL-C value based on this categorization. Ninety-three Users over-reported (self-reported LDL-C greater than measured LDL-C), and 69 Users under-reported (self-reported LDL-C less than measured LDL-C). Thus, more Users over-reported than under-reported their LDL-C value. Of the 367 Users who self-reported their LDL-C within 130-170 mg/dL, 250 (68.1%) had a measured LDL-C value in the 130-170 mg/dL range.

Although participants in CUSTOM were not required to know their Total-C in order to be eligible for MEVACOR™ OTC, 855 of the User population had both a known self-reported Total-C value and a non-missing measured total-C from the evaluation performed at the study site. The results from each were categorized using 3 categories: <200 mg/dL, 200 to 240 mg/dL, and >240 mg/dL. A total of 663 (77.5%) of the 855 had a self-reported Total-C that agreed with the measured Total-C value based on this categorization. Ninety-one Users over-reported (self-reported Total-C greater than measured Total-C), and 101 Users under-reported (self-reported Total-C less than measured Total-C). Thus, slightly more Users under-reported than over-reported their Total-C value. Of the 347 Users who self-reported their Total-C within 200 to 240 mg/dL, 245 (70.6%) had a measured Total-C value in the 200 to 240 mg/dL range.

3.2.2 Nonprescription Lovastatin 10 mg Studies

Cholesterol Recall Accuracy

The accuracy of cholesterol recall was also assessed in the lovastatin 10 mg Protocols 076 (Pharmacy, 1997-1998) and 079 (Restricted Access, 1998). Participants were asked to identify the numeric category that best described their Total-C values, and this recall was compared to the participant's measured Total-C from the desktop evaluation performed at the study site. The numeric categories in Protocol 076 were <200, 200 to 240, and >240 mg/dL and in Protocol 079 were <190, 190 to 250, and >250 mg/dL. The reason for permitting a slightly wider window in Protocol 079 had to do with differences in study design, not in the intended criteria for OTC eligibility. In Protocol 079, only respondents who said their Total-C was between 190 and 250 mg/dL were given an appointment to the site for further screening including lipid testing. With both studies combined, there was a cohort of ~2,500 participants who said their Total-C was within the range of 200 to 240 mg/dL (Protocol 076) or 190 to 250 mg/dL (Protocol 079).

In the Restricted Access Study (Protocol 079), 61.5% of the 1,149 participants who self-reported their Total-C within 190 to 250 mg/dL were correct based on a tested range of 190 to 250 mg/dL. Of the remaining participants in this category, 31.8% underestimated their Total-C (test results >250 mg/dL), and a smaller number (6.7%) overestimated their Total-C (test results <190 mg/dL).

Similar results were found in the Pharmacy Study (Protocol 076), where 56.1% of the 1,351 study participants who reported that their Total-C was within the range of 200 to 240 mg/dL were correct based on test results that fell within the range of 190 to 250 mg/dL. The remaining individuals in this 200 to 240 mg/dL self-report category fell outside the range upon testing: 39.9% underestimated their Total-C (test results >251 mg/dL) and 4% overestimated their Total-C (test results <190 mg/dL).

The Pharmacy Study (Protocol 076) also provided additional information on cholesterol self-report in 2 other numeric categories of cholesterol awareness, i.e., >240 mg/dL and <200 mg/dL. An analysis of the recall data showed that 88% of participants (N=1,247 of 1,416) who thought their cholesterol was >240 mg/dL (highest cholesterol numeric category) were in fact correct based on their tested cholesterol values within 10 mg/dL. For participants who placed their cholesterol in the lowest category (<200 mg/dL), 41.5% of these participants (39 of 94) were found to have accurate recall based on testing to <190 mg/dL. The remaining participants had actual total cholesterol values which were higher: 36.2% had a value of 200 to 240 mg/dL and 22.3% had a value >240 mg/dL.

3.2.3 Summary

These data support the conclusion that product advertising and labeling are effective at directing the majority of consumers to know their lipid values before making a product purchase decision, or to consult with a physician before beginning to use nonprescription lovastatin. In addition, the data from CUSTOM and the lovastatin 10-mg studies were consistent in showing that consumers' knowledge of LDL-C and Total-C is sufficiently accurate to support appropriate purchase and use decisions.

3.3 Self-Selection (Initial Use Decision)

The challenge in developing effective labeling and product promotion for nonprescription lovastatin is to guide eligible people into appropriate long-term use of the product while guiding ineligible people into physician care as appropriate, or merely into a healthy lifestyle of diet and exercise if medication is not needed. Three of the Actual Use studies in the nonprescription lovastatin development program were designed to assess the self-selection behavior of consumers in response to the product labeling: CUSTOM Study (Protocol 084), Pharmacy Study (Protocol 076), and Red Arrow Study (Protocol 081).

The primary focus of this section is on data from the CUSTOM Study since it represents the current treatment paradigm, product labeling and support materials. However, data from Protocol 081 will also be presented since it is close in design to the CUSTOM Study (e.g., "all comers" design, storefront setting, product purchase requirement, cholesterol testing available at the study site to aid in the purchase decision, ineligible participants could purchase and use the product, toll-free service for eligibility verification).

3.3.1 CUSTOM Study (Protocol 084)

This study was primarily designed to evaluate the effectiveness of the MEVACOR™ OTC Self-Management System in guiding consumer behavior. Two facets concerning consumer behavior are of primary interest in this study. One is the initial self-selection decision to use the product. The second is the ongoing decision process regarding continued use (de-selection).

The data collected in this study included the actual decisions of the participants regarding initial use (self-selection) and continued use (de-selection) as well as information about the participant that allowed an assessment of these decisions.

The initial self-selection decision to use involves the assessment of label benefit criteria that target the correct population (age, LDL-C, other risk factors) and label safety warnings for individuals who have contraindications (existing medical conditions or prohibited medications) that could put them at increased risk from using the product.

The de-selection decision process begins after the initial decision to use the product and continues throughout the ongoing use of the product. This decision process involves the assessment of label benefit criteria directing the consumer to obtain a follow up cholesterol test and evaluate whether the LDL-C goal is achieved. The de-selection decision process also involves the assessment of label safety warnings directing the consumer to discontinue drug and/or speak with doctor when beginning a new prescription medication or upon developing a new medical condition or unexplained muscle pain.

Figure G-2 depicts the four quadrants of the label described in the above paragraphs.

Figure G-2
Label Benefit Criteria and Safety Warnings

Safety Warnings – Initial Use ▪ Pregnant/breast feeding ▪ Liver disease ▪ Previous muscle pain ▪ Interacting meds ▪ Rx Lipid-lowering therapy	Benefit Criteria – Initial Use ▪ Age ▪ Lipids ▪ Risk Factors
Safety Warnings - Ongoing Use ▪ New Rx ▪ New medical condition ▪ Unexplained muscle pain	Benefit Criteria – Ongoing Use ▪ Follow up Lipid Test ▪ LDL-C Goal

The first assessment of de-selection was at Week 6 when a user should have obtained a follow-up lipid test and made a decision about reaching LDL-C goal. Another assessment of de-selection occurred at Week 26 after the study ended. Users could elect, at any time, to continue or discontinue therapy.

For assistance in making self-selection and de-selection decisions, the product carton label encouraged interactions with healthcare professionals (personal physician, study physician, or pharmacist or study personnel playing the role of a pharmacist). Any reports by a participant of an interaction or consultation with a physician or other healthcare professional regarding their initial decision to use MEVACOR™ OTC, or a continued use decision regarding new medications, new medical conditions, an occurrence of muscle pain and not reaching LDL-C goal were collected on the participant's record. If participants reported that they talked to a physician, this information could mitigate behavior that was otherwise not according to label (e.g., self-selection to use MEVACOR™ OTC with a baseline LDL-C of 181 mg/dL [too high] and reported talking to the doctor). In addition, specific occurrence and timing of an interaction with a healthcare professional was a required behavior as directed by the label (e.g., diagnosis of a new medical condition such as high blood pressure requires physician interaction). In such cases where a participant self-reported an interaction or

consultation with a physician regarding the use or continued use of MEVACOR™ OTC, either because they had a reason for ineligibility or a reason to stop taking drug, the participant's behavior was assessed as According to Label (see below) since this was consistent with labeled directives.

Based on the information collected from the participants, decisions were assessed on the day of first dose and at Weeks 6 and 26 (initial self-selection and de-selection decisions jointly), and were classified, according to the Data Analysis Plan (DAP), into one of four ordinal categories.

The categories are:

> **According to Label, Medically Acceptable for Self-Management (AL-MASM)**—This category represents a decision that is entirely consistent with the product label. It includes participants with reasons for ineligibility or for possible discontinuation, who consulted with a doctor about their use of MOTC as directed by the label. In addition, specific information, obtained from the participant's answer to an open-ended question, was used to mitigate behavior that was otherwise not according to label.
>
> **Adequate Benefit, Medically Acceptable for Self-Management (AB-MASM)—**This category represents a decision that is not entirely consistent with the product label but use of the product still provides some benefit to the individual.
>
> **Not Adequate Benefit, Medically Unacceptable for Self-Management (NAB-MUSM)—**This category represents a decision that is not consistent with the product label and that deviates sufficiently that it allows potentially inadequate therapeutic benefit but without imparting undue potential safety risk. Some participants were placed in this category to self-manage their cholesterol levels either because their CHD risk was too low or too high.
>
> **Not Adequate Safety, Medically Unacceptable for Self-Management (NAS-MUSM)—**This category represents a decision that significantly deviates from the label directions, creating potential safety risks despite potential therapeutic benefit. It would be medically unacceptable for participants in this category to self-manage their cholesterol levels because of inappropriate safety decisions.

This categorization, at self-selection, through Week 6 and Week 26 de-selections, was the endpoint for the study. In discussing the possible outcomes from this study, the above 4 categories were further refined into 2 categories: (1) **Medically Acceptable for Self-Management (MASM)** combines the first 2 categories and (2) **Medically Unacceptable for Self-Management (MUSM)** combines the last 2 categories.

Using this approach, any single deviation (regardless of whether it concerned potential safety risk or therapeutic benefit) from any label element disqualified the participant from being categorized as "according to label" (AL) and, depending on the magnitude of the deviation(s), resulted in categorization as "adequate benefit" (AB), "not adequate benefit" (NAB), or "not adequate safety" (NAS). The algorithm jointly considered all items detailing the criteria and label directives when assessing behavior. Potential safety risks were considered prior to any assessment based on benefit. Thus, a participant incurring potential safety risk obviated any consideration of benefit.

The hypothesized benchmarks for MASM behavior and the realized proportions for MASM behavior are presented in the first three columns of Table G-6. The 95% confidence intervals are approximately ± 3.0% for each decision. This approach, specified in the DAP, yielded results that did not meet the hypothesized benchmarks. Therefore, further investigation was necessary in order to understand consumer behavior.

An alternative approach, in which participant decisions around each individual element of the product label, is also presented. These post-hoc analyses, referred to as the Complementary Assessment of Benefit and Safety or CABS, independently assessed behavior based on levels of adherence to specific benefit-related criteria and specific safety-related criteria. In this approach, behavior associated with benefit was assessed even if the participant incurred potential safety risks. In this way, the CABS approach can examine off-label behavior and determine whether a reasonable degree of benefit was still achieved without detracting from optimal safety. This is especially important when assessing behavior that resulted in the User being categorized as NAB or NAS in the DAP approach. Safety was similarly evaluated independent of benefit.

The CABS approach, also presented in Table G-6, indicates that a slight majority (53 - 66%) of participants adhered or closely adhered to label benefit criteria whereas an overwhelming majority (90-94%) did not incur potential safety risk. Almost all inappropriate behavior was attributable to non-adherence to label benefit criteria, not safety criteria. A comparison of the pre-specified analyses to the supplemental CABS analysis is presented in Figure G-3.

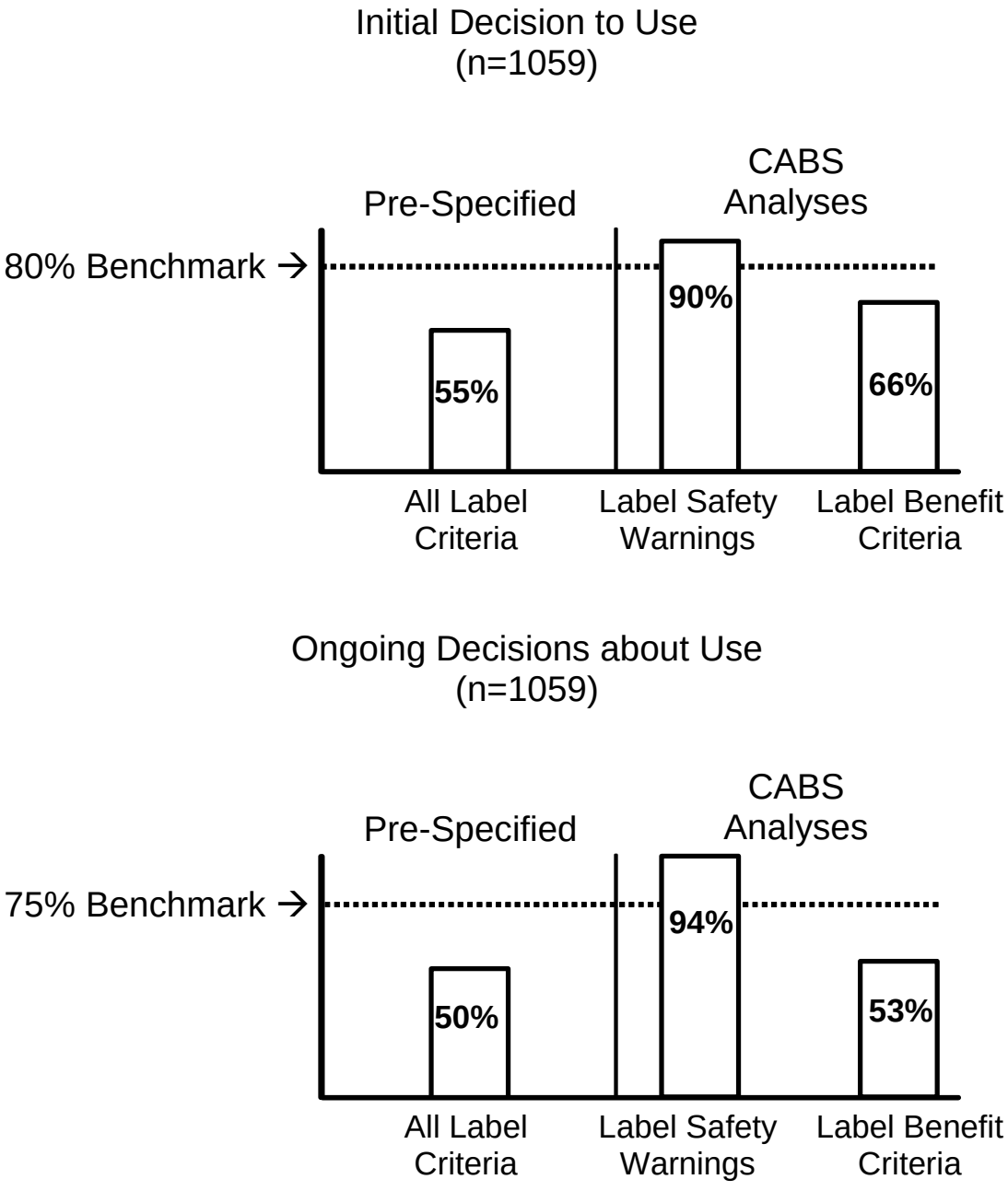
Table G-6

Analysis of Participant Behavior by Decision Time Interval
(Users)

Decision	Benchmark	Analysis Approach		
		DAP	CABS	
		Percent Assessed as MASM[†]	Percent Adhering or Closely Adhering to Label Benefit Criteria	Percent Not Incurring Increased Potential Safety Risk
Self-selection	80.0	55.1 (571/1037)	65.8 (687/1044)	89.6 (935/1044)
De-selection through Week 6	75.0	41.3 (409/990)	NA	NA
De-selection through Week 26	75.0	50.1 (494/986)	53.3 (499/936)	94.3 (345/366)

NA = Not Applicable, CABS=Complementary Assessment of Benefit and Safety, MASM=Medically Acceptable for Self-Management.
[†]95% Confidence Interval is approximately ± 3..0%

Figure G-3


Initial Decision to Use
(n=1059)
Pre-Specified
CABS Analyses
80% Benchmark →
55%
90%
66%
All Label Criteria
Label Safety Warnings
Label Benefit Criteria
Ongoing Decisions about Use
(n=1059)
Pre-Specified
CABS Analyses
75% Benchmark →
50%
94%
53%
All Label Criteria
Label Safety Warnings
Label Benefit Criteria

Results in the following sections are presented item by item into behavioral groupings consistent with ATP III guidelines and described by the participants' degree of adherence to the label benefit criteria or safety warnings.

Overall Assessment and Potential for Benefit

As noted in Table G-4, 3,346 participants traveled to the study sites. Of these, 3,316 examined the MOTC carton label and support materials and made a decision about purchasing and using the product (Evaluators). The Evaluators are likely to be representative of the population that would be interested in MOTC in the actual marketplace. This population from the CUSTOM trial demonstrates that the Self-Management System is successful in guiding consumers to make an appropriate initial use decision.

There were 2,111 Evaluators who did not purchase the product (Non-Purchasers). The Non-purchasers fall into one of two subgroups: those who decided not to buy (n=1,673) and those who were defaulted to Non-Purchasers because they needed more information and never gave a final decision regarding purchase (n=438). Of the 1,673 Evaluators who decided not to buy (Does Not Want to Buy subgroup), 98% (1,634/1,673) were ineligible by labeled criteria.

There were 94 Evaluators who purchased the product but did not use it (Purchaser, Non Users) either because they were not dispensed drug (n=30) or they brought it back unused (n=64). The 2 most common reasons participants returned drug before using it were that they were advised not to use it by their doctor (n=26) or they learned MEVACOR™ OTC was not appropriate for them (n=17).

Of the 1,059 Evaluators who purchased and used the product (Users), a total of 687 adhered or closely adhered to the label benefit criteria when making their initial decision to use. Therefore, 86% of the Evaluator population (n=3,316) adhered or closely adhered to the label benefit criteria when making their initial decision to use (n=687) or chose not to use the product (n=2,111+64).

Potential for benefit from MOTC was not limited to those 687 users who adhered or closely adhered to the restrictive MOTC label, but was also seen among most of the 357 Users who did not adhere to the label benefit criteria. Although 188 of these 357 Users did not know their complete lipid profile, 93% (175 of 188) had an elevated LDL-C (>130 mg/dL) or Total-C (>200 mg/dL). Over 72% of this cohort (at least 258 of 357) were eligible for statin therapy according to ATP III guidelines. Thus, 89% (945 of 1,059) of Users could benefit from statin therapy either by their adherence or close adherence to the CUSTOM label (n=687) or via their eligibility for treatment with statins by ATP III guidelines (n=258). Many Users knew their cholesterol was elevated and appropriately elected to use MOTC despite not having a complete knowledge of their entire lipid profile. By requiring consumers to know their HDL-C, LDL-C and triglycerides, the carton label may have been overly restrictive with respect to this heterogeneous group of individuals.

There were 167 high risk Users with a history of CHD, stroke, or diabetes; 70 used the product without first checking with a physician (did not adhere to label benefit criteria). The majority (46 of 70; 66%) was not on a lipid lowering drug at the time of self-selection, but should have been according to current ATP III guidelines. Over one-third (26 of 70; 37%) reported a physician interaction regarding MOTC during the study.

Eleven (11) of the 357 Users who did not adhere to the label benefit criteria indicated that they substituted MEVACOR™ OTC for a prescription cholesterol-lowering medication.

One hundred seventy (170) of the 357 Users did not adhere to the label benefit criteria because they had a self-reported triglyceride ≥200 mg/dL. This was based on a non-fasted triglyceride evaluation in 95 of the 170 individuals (resulting in a potential elevation of serum triglycerides). The median reported serum triglyceride value for the group with self-reported triglycerides >200 mg/dL was 291 mg/dL. The majority (125 of 170; 74%) had reported triglyceride values below 400 mg/dL, but 26% (45 of 170), had triglycerides ≥400 mg/dL. Both LDL-C and Total cholesterol levels (self-reported values) for the group were elevated; median LDL-C 146 mg/DL and median Total cholesterol 253 mg/dL.

Evaluators were not required to calculate or know their 10-year CHD risk score when making a decision to use MOTC; however, in order to characterize the User population, the CHD risk of Users was calculated (this information was not shared with the Users). Two subsets of Users had lower CHD risk than targeted by the MOTC label. One group of Users (289 of 1,059; 27%) were at lower calculated 10-year CHD risk (<5% ten-year risk). However, of these 289 lower risk Users, 76 (26%) had 2 or more CHD risk factors and were considered to be eligible for statin therapy by ATP III guidelines. This group had other explanatory factors, including LDL-C ≥130 mg/dL (73% of lower risk Users), Total-C ≥200 mg/dL (87% of lower risk Users), at least one CHD risk factor (72% of lower risk Users), and interaction with a physician (47% of lower risk Users). The second subset of lower risk Users (n=19) had a self-reported baseline LDL-C value below 130 mg/dL and did not consult with their physician before using MOTC. This second subset represents fewer than 2% of all Users. Thus, lower risk populations can also derive some benefit from additional LDL-C lowering. Therefore, deviation in this direction from the criteria defined by the MOTC label tested in CUSTOM still allows for potential benefit, despite being below the 10% to 20% ten-year CHD risk group targeted by the OTC label criteria.

Potential for Safety Risk

This section examines behavior that was not consistent with optimal safety according to the directions stated in the MOTC label and may increase the potential for an adverse event.

There were very few potential safety risks at the time of self-selection. According to the Data Analysis Plan and a strict interpretation of the MOTC label, 109 of the 1,059 Users were originally categorized as Not Adequate Safety, Medically Unacceptable for Self-Management (NAS-MUSM). However, certain participant responses to eligibility and behavior questions did not provide sufficient insight to properly evaluate the observed behavior. Therefore, specific subgroups were identified for contact with follow-up questions that were intended to clarify the initial responses. The subgroups identified were users of MEVACOR™ OTC who, as part of the eligibility assessment, reported previous muscle pain from cholesterol-lowering medicine, concomitant use of prescription lipid-lowering medication with MEVACOR™ OTC, or current liver disease, and had not consulted with a physician prior to use of MEVACOR™. Additional information received from these Post-CUSTOM Clarification Questions reduced the number of Users who exhibited behavior associated with a potential safety concern from 109 to 23 (2%) at the time of self-selection.

Risk for developing Myopathy

None of the cases of potential safety concern were associated with a reported case of myopathy. Of the 109 initial use decisions with potential for sub-optimal safety, 53 were decisions to use MOTC despite a self-reported history of previous muscle pain, weakness, or tenderness from taking a cholesterol-lowering medication. This warning is included as a conservative measure in the MOTC label, although neither the ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins nor any other recent report suggests such a history as a risk factor for developing statin-associated myopathy [5; 51; 102; 138]. Furthermore, musculoskeletal complaints are commonly seen among adults. The annual skeletal pain visit rate in the United States for Year 2000 was 280 visits per 1000 people. Musculoskeletal pain visits accounted for 9.9% of all visits in Year 2000 [137]. Although none of these 53 users reported the development of myopathy during the study, 13 did report muscle pain, weakness, or tenderness judged to be drug related. Ten of the 13 behaved appropriately by discontinuing the drug (n=10) and/or talking to their physician about MOTC (n=6). Overall, 28 of the 53 (53%) Users with a self-reported history of previous muscle pain, weakness, or tenderness from taking a cholesterol-lowering medication had a physician interaction regarding MOTC during the study and 27 of the 53 (51%) remained in the study for at least 168 days (24 weeks), without incident.

Potential for Drug Interactions

Among the 3,316 Evaluators of the MOTC-SMS, there were 152 participants (4.6%) who reviewed the product and reported taking potentially interacting drugs. Of these 152, 10 participants decided to use MOTC without consulting with a physician. In addition, of the 44 Evaluators reporting they were unsure if they were taking a potentially interacting medication, 6 were among the 1,059 Users choosing to take MEVACOR™ OTC without consulting with a physician.

None of these 10 individuals who initially made a self-selection decision to use MOTC concomitantly with a potentially interacting medication developed a drug-related muscle adverse experience (including myalgias and muscle weakness). Of these 10 Users, 5 were still taking MOTC at week 26 when the study ended.

Most of the Users taking niacin and gemfibrozil were recontacted after study completion (via the Post-CUSTOM Study Clarification Questions). Of the 7 recontacted Users reportedly on niacin at the time of self-selection, 6 stated they had stopped the niacin upon starting MOTC and one stated he had never used niacin. Of the 2 recontacted Users reportedly on gemfibrozil at the time of self-selection, both stated that they had stopped the drug before beginning MOTC.

Actual Safety

MEVACOR™ OTC mg was well tolerated in the CUSTOM User population. Adverse event rates were comparable to those seen in placebo-controlled, randomized clinical trials of lovastatin 20 mg. There were no reports of myopathy or rhabdomyolosis, and no reports of hepatitis or liver failure. No new safety issues were identified. More details on the safety profile of lovastatin 20 mg in CUSTOM can be found in Section E. Safety of Lovastatin of this Background document.

3.3.2 Red Arrow Study (Protocol 081)

Of the 2,416 participants who came to the study site and made a product purchase decision, 272 (11%) decided not to purchase the product because they were not interested, and 903 (37%) decided that they needed more information before deciding to purchase.

Prevalence of Label Exclusions in Participants With Medical History

Of the 2,416 participants who made a product selection decision, 2,264 provided their medical history. The situations where consumers should decide not to purchase the product (provided on the carton label) are grouped for review of results into 4 label exclusion categories: (1) participants whose only reason for ineligibility was total cholesterol >240 mg/dL; (2) participants with conditions indicating higher CV risk, i.e., history of CHD, stroke, diabetes mellitus (DM), or hypertension (HTN); (3) participants subject to 1 or more of the 4 safety warnings (allergy to lovastatin, current liver disease, taking potentially interacting drugs, <1 year postmenopausal); and (4) "other," a heterogeneous group with a variety of exclusions. The reasons for ineligibility in the "other" group were: males <40 years old, total cholesterol <200 mg/dL, did not know total cholesterol value, past history of liver disease, and those consumers taking prescription or OTC cholesterol-lowering drugs or who did not know if they were taking cholesterol-lowering drugs.

Correctness of Product Selection Decision in Participants With Medical History

Table G-7 displays the percents of participants in each of the 4 label ineligibility categories who made the correct product selection decision (decided not to purchase) after only reading the outside carton label, and again after reviewing both the carton label and label reinforcement tools contained in the package. In each of the label ineligibility categories, the percentages of participants making the correct decision not to purchase the product increased after participants reviewed the label reinforcement tools.

Table G-7

Study 081—Correctness of Product Selection Decision
by Label Ineligibility Category

Label Ineligibility Criteria	N	Correct After Reading Carton Label (Outside)	Correct After Label Reinforcement Tools (Inside)
Total cholesterol >240 mg/dL only	381	54%	72%†
Higher CV risk (CHD, stroke, DM, HTN)	262	68%	83%†
Safety warning (total)	120	68%	84%
"Do Not Use" medications	83	70%	83%
Other	604	70%	85%†

† Included toll-free service.

Toll-Free Eligibility Verification Service

The toll-free eligibility verification service was effective in influencing ineligible participants who purchased the product to reverse their initial decision. Approximately two-thirds (90 of 146, 62%) of ineligible participants who called the toll-free service subsequently stopped taking drug by their return visit (Week 4). In contrast, only about one quarter (61 of 230, 26%) of ineligible participants who did not call the toll-free service subsequently stopped taking drug by Week 4. For comparison, the proportions of eligible participants who stopped taking drug by Week 4 were similar for those who called (9%) and those who did not call (11%). These results indicate that, in the ineligible people who went home with product, use of the toll-free service substantially improved the accuracy of the product selection process compared to the carton materials alone.

3.3.3 Summary of Self-Selection Results

Results from the CUSTOM Study and the Red Arrow Study are generally similar, and demonstrate that:

- The majority of consumers who evaluate nonprescription lovastatin appropriately choose whether or not to use the product
- Self-selection decisions to use nonprescription lovastatin that involve a potential for safety risk are rare
- Inappropriate self-selection is often mitigated by interaction with a physician or by components of the MOTC-SMS (e.g., the toll-free number for eligibility verification).

The Pivotal Label Comprehension and CUSTOM studies provide complementary information about consumer interpretation of the MEVACOR™ OTC carton label. Despite substantial differences in objectives and methodology, the results of the 2 studies taken together lead to the following conclusions:

- Although complex and with multiple messages, the MEVACOR™ OTC label is still comprehensible to a diverse audience. However, while consumers do understand the intentions of the label, CUSTOM shows that people make decisions based not only on the label information but also on other factors unique to their own particular situation. In the great majority of cases, these decisions do not lead to a safety concern and may in fact provide meaningful benefit to the product user.
- The label prevents serious self-selection errors. In both studies, the messages directing potential users to a health care professional if they had questions about their appropriateness were taken seriously. In the Pivotal Label Comprehension Study (Pivotal LCS), this was apparent by the fact that respondents were able to discriminate between situations when a person would need to talk to a doctor versus when they could start using the product immediately. Additionally, 90% of Pivotal LCS respondents felt they could not use the product immediately or that they would talk to a doctor first. Similarly, in CUSTOM most Evaluators did not choose to buy the product, and a high proportion of Evaluators actually talked to a doctor before or during product use. Therefore, CUSTOM corroborated self-reported intentions in the Pivotal LCS.

3.4 Self-Management of Treatment Over Time

CUSTOM Protocol 084 was the only Actual Use study in the nonprescription lovastatin development program with an objective to evaluate participant decisions regarding continued use. In addition, consumer behavior regarding obtaining a new prescription medication, being diagnosed with a new medical condition, and developing unexplained muscle pain was supplemented with de-selection scenario questions at the end of the study. Therefore, the data summarized in this section are from the CUSTOM Study only.

3.4.1 Behavior Regarding Follow-Up Cholesterol Test

Most Users (782 of 1,059; 74%) either obtained a follow-up lipid profile (n=666) or discontinued from the study prior to the recommended timeframe for obtaining a follow-up test (n=116). In addition, over half of Users whose behavior could be assessed (53%; 499 of 936) adhered or closely adhered to the label criteria regarding the follow-up test, interpreting the results regarding LDL-C goal, and in deciding to continue or discontinue use of MOTC.

Of the 277 Users who did not obtain a follow-up lipid profile and continued in the study past the recommended timeframe for obtaining a follow-up test, an end of study LDL-C value was available for 201. Of these, 55% (111 of these 201) achieved LDL-C target goal of <130 mg/dL. It is likely that this group would ultimately obtain a cholesterol test in the future, since only 2% (9 of 398) of Users who participated in the Post-CUSTOM Survey reported never having had a cholesterol test. Also, from the end-of-study questions 70% (533/762) of Users who provided a response reported that it was very likely that they would get another test in one year or sooner, and an additional 22% (171/762) said they would get one at their next doctor visit. This suggests that many consumers still view the physician as their preferred option for obtaining lipid values.

Lipid-lowering Efficacy—End-of-Study Cholesterol Test

Efficacy of lovastatin 20 mg in an OTC setting was evaluated by percent change from baseline of LDL-C, and the number of Users achieving LDL-C goal of <130 mg/dL at the end of the CUSTOM study. After 26 weeks, median fasting LDL-C was reduced by 25%, and 62% of Users achieved the target goal of LDL-C <130 mg/dL. The LDL-C reduction from baseline was similar to that observed in randomized controlled trials of lovastatin 20 mg. More details on the efficacy of lovastatin 20 mg in the CUSTOM study can be found in Section C. Efficacy and Benefit of Lovastatin of this Background document.

3.4.2 Management of Potential Safety Risks

Potential for Drug Interactions

During the study, only 2 of the 1,059 users were given new prescriptions for a potentially interacting medication and did not talk to their doctor. Both were prescribed clarithromycin; both correctly stopped MOTC when they began taking the antibiotic.

Changes in Health Status

There were 366 Users that experienced either a new medical condition or began a new prescription. Of these, 345 (94%) adhered or closely adhered to the label directions regarding the continued use of MOTC and informing a physician. Of the 21 Users that did not adhere to the label criteria, only 9 had the potential for safety concern. The remaining 12 were explainable. Two (mentioned above under Potential for Drug Interactions) were given new prescriptions for a presumed infection (clarithromycin);

both correctly stopped taking MOTC when they began taking the antibiotic. Three developed CHD, diabetes, or stroke and did not inform their physician about MOTC; 2 had a valid reason for not doing so. The remaining 16 Users developed unexplained muscle pain and neither discontinued MOTC or informed their physician about MOTC; 8 provided a reason for not discontinuing or informing a physician (2 said they did talk to a doctor, 2 knew the cause of their muscle pain, 1 stated that the problem stopped after a short time, 1 stated the problem was minor, and 2 provided a reason categorized as "other").

As part of the CUSTOM protocol, scenario testing was conducted at study end. When shown a scenario where a new prescription was given for a potentially interacting medication, 90.8% of Users who answered the question (877/966) gave a medically acceptable response. When shown a scenario where a new medical condition was diagnosed, 98.4% of Users who answered the question (950/965) gave a medically acceptable response. Finally, when shown a scenario that described the development of unexplained muscle pain, 81.3% of Users who answered the question (785/966) gave a medically acceptable response (i.e., they would stop using the product, talk to a doctor, or both). This is similar to the behavior among Users in CUSTOM who actually developed unexplained muscle pain and acted appropriately (47/63; 75%). Those who gave an inappropriate response (19% and 25% in the scenario and Actual Use, respectively) may reflect the fact that muscle aches and pains, even if there is no explainable cause, are a common occurrence for many people and generally do not warrant a visit or call to their physician. Participants may have had varying interpretations of the label term "any unexplained muscle pain, weakness, or tenderness" and applied their own experience to these scenarios and decided that a call to a doctor would be justified only if the pain intensified or did not go away after a period of time.

3.5 Interactions with Health Care Professionals

Cholesterol management has been generally viewed as requiring the involvement of a physician in the context of the entire medical management of the patient. The ultimate goal of consumer interactions in the OTC environment is to establish a partnership in the management of cholesterol. Although physician interactions were encouraged by the MOTC-SMS, it is realistic to recognize that self-motivated consumers might attempt to manage cholesterol on their own.

3.5.1 CUSTOM Study (Protocol 084)

Figure G-4 visually depicts some of the key results regarding participant interactions with physicians.

Physician interactions were reported by 42% of Purchasers before beginning therapy with MOTC and by 57% of all Users (at any time during the study). In addition, 46% of Non-Purchasers reported that they intended to talk to their doctor regarding cholesterol management and MOTC. Twenty-two percent (22%) of the Non-Purchasers reported that they did in fact talk to their doctors prior to making a decision to not buy the product.

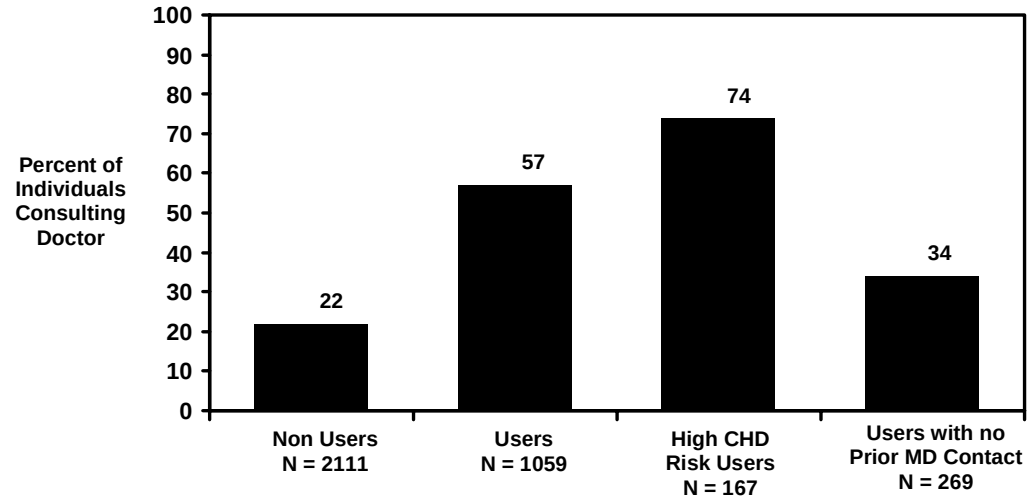
In some cases, these physician interactions likely indicate a strong interest in taking MOTC to lower cholesterol despite the restrictive labeling and relatively complex self-management rules.

The MOTC Self-Management System led to physician interactions for 34% (n=92) of the 269 users who had not recently or ever talked to a doctor about cholesterol-related issues. Thus, the MOTC-SMS successfully directed many cholesterol-concerned individuals into the health care system who may not have had such physician contact otherwise.

Also, although clearly recognized by the MOTC label as being inappropriate for OTC therapy without first consulting with a physician, it was previously noted that 70 high risk Users (i.e. those with a history of CHD, stroke, or diabetes) decided to take MOTC. Twenty-six of the 70 (37%) ultimately interacted with a physician during the study. An additional 97 such high risk Users demonstrated appropriate behavior by consulting with their physician before beginning to use MOTC. Thus, 74% (123 of 167) of high risk Users interacted with a physician during CUSTOM.

Figure G-4

CUSTOM: Physician Interactions



Results from CUSTOM provide evidence that the MOTC-SMS helped to direct Evaluators considered by the label to be ineligible for MOTC with either LDL-C >170 mg/dL or triglycerides >200 mg/dL to seek professional care. As part of the MOTC-SMS, these Evaluators received a referral (advice and a letter) to consult with their physician, and 58 provided follow-up survey information. Thirty-two (32) of these 58 reported that they talked to a physician about cholesterol within a few months of getting the referral. Many of them (19/32) also received a prescription for lipid lowering therapy. Even without a referral, the MOTC-SMS successfully motivated Evaluators with elevated LDL-C >170 mg/dL or triglycerides >200 mg/dL to talk to a physician. Of the 1,146 Evaluators with either LDL-C >170 mg/dL or triglycerides >200 mg/dL who considered purchasing MEVACOR OTC, 359 (31%) reported that they spoke with a physician at the time of their self-selection decision (176/664 Non-Purchasers and 183/482 Purchasers).

Finally, the Post-CUSTOM survey showed that 54% (75/139) of those who reported that they did not meet the LDL goal said they talked to a doctor, and an additional 20% (28/139) had made a doctor appointment which had not yet occurred at the time of the survey [139]. Of those who saw a doctor, 75% were given a new treatment plan (56/75), nearly all of which included a prescription (55/56).

The high level of physician interaction among participants in CUSTOM may be explained by User information collected from the Post-CUSTOM Survey. Of the 360 participants in the survey who used other OTC products, 82% (n=296) believed that MEVACOR™ OTC treated a more serious health problem than other OTC products and many consulted with their physician on a frequent basis (88% visited their doctor at least once a year, 56% visited their doctor more frequently than once a year, and 40% [158 of 398] felt strongly about the need to check with their physician before making most healthcare decisions).

3.5.2 Lovastatin 10-mg Actual Use Studies

The results regarding physician interactions from CUSTOM are supported by findings from the nonprescription lovastatin 10-mg use studies. About half of all study participants in Protocols 076 (Pharmacy) and 081 (Red Arrow) said they would talk to their physicians before self-treatment. In Protocol 076, nearly a third (30%) of enrolled participants who returned to the study site after only 8 weeks said they had in fact discussed participation in the study with their physicians, even though they had been screened for medical history and cholesterol levels by the pharmacist investigator. In a market research survey conducted at the final visit in Protocol 076 (Pharmacy), 403 participants were questioned about interaction with their personal physician, and 195 (48%) indicated that they spoke with their personal physician about nonprescription lovastatin 10 mg.

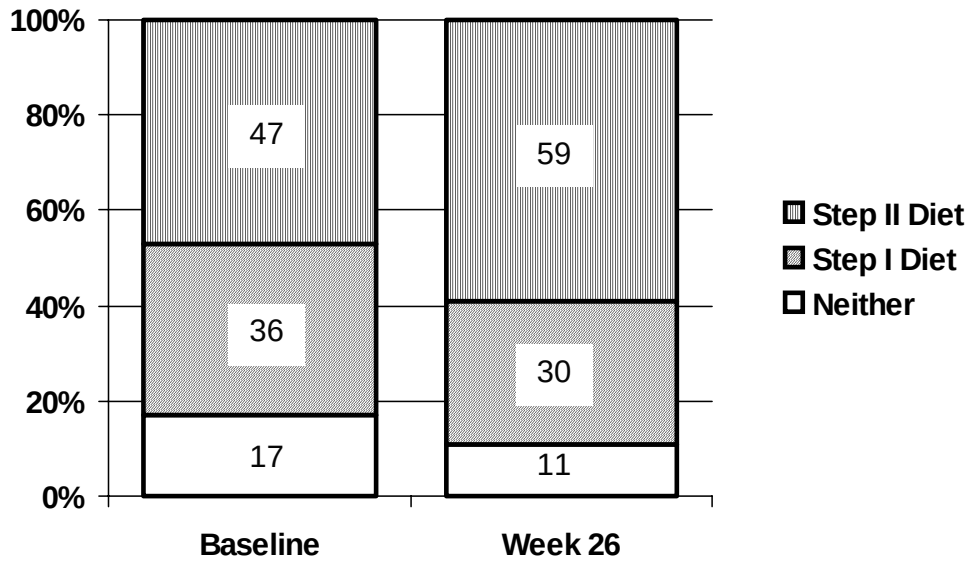
3.6 Heart-Healthy Lifestyle Behaviors

3.6.1 CUSTOM Study (Protocol 084)

Heart-healthy behavior was evaluated through questionnaires and application of a MEDFICTS dietary assessment. Although 80% of Users reported they had already tried heart-healthy lifestyle changes before beginning MOTC, 40% reported an improvement in diet, and 24% reported an improvement in exercise habits during the study. At baseline, 83% of users were already on an American Heart Association (AHA) Step I or II diet (by MEDFICTS). By study end (Week 26), 27% of users had further improved their diet (by MEDFICTS), with 56% of those not already on an AHA diet improving to a Step I or II diet, and 48% of those already on a Step I diet improving to a Step II diet (see Figure G-5).

Figure G -5

CUSTOM Results
Heart-Healthy Lifestyle Behaviors Improve
Dietary Habits*



*Diet assessed with MEDFICTS.

Among the 398 Users that responded to the Post-CUSTOM Study Survey, over half said they made positive change in lifestyle or heart health behaviors or planned to make one soon; and of those, the majority (77%) said the MOTC-SMS was a key influence toward improving that behavior. Thus, the concept of self-management of cholesterol extends beyond drug therapy and affects lifestyle habits as well when a motivating education and support system is employed.

Participants demonstrated a significant degree of interest in the MOTC Self-Management System materials (available to all Users) and Heart Health Program (offered only to label-appropriate Purchasers). Over 60% of participants who looked at the package (610 of 903; 68%), Quick Start Guide (529 of 828; 64%), and Booklet (451 of 727; 62%) felt them to be very useful. Of those who were in the Heart Health program and indicated that they received the newsletters, 38% (70 of 186) felt them to be very useful. In the end-of-study questionnaire data, 258 participants indicated that they joined the Heart Health Program and an additional 240 participants said that they tried to join but were

rejected. (Prior to enrollment in the Heart Health Program, an eligibility assessment was administered. Ineligible Users were denied enrollment in the Heart Health Program, and received a message to discontinue MOTC and return the product for a refund.) Therefore, based on the end-of-study questions, 51% of participants expressed interest in receiving more information about MOTC and cholesterol lowering. Many interested participants were not allowed to join as per the CUSTOM protocol, but, in retrospect, it seems reasonable that the Heart Health Program could be an important vehicle in the marketplace to help guide appropriate product usage or physician interaction. Therefore, the Heart Health Program should be expanded to allow access to all interested consumers, not just those that exactly fit the restrictive label criteria.

3.6.2 Pharmacy Study (Protocol 076)

The diet and exercise behavior data from CUSTOM are consistent with the findings from participants in the nonprescription lovastatin 10-mg Pharmacy Study (Protocol 076). In a market research survey conducted at the final visit in the Pharmacy Study, participants were questioned about their diet and exercise habits during the clinical study. Of the 403 participant responses received, 91% stated that their diet was the same or healthier (51%, 40%, respectively) during the study than before the study, and 94% said they maintained or improved their exercise habits (76%, 18%, respectively). Thus, participants in the market research survey gave no indication of using lovastatin 10 mg as an excuse to lessen their adherence to a healthy lifestyle.

3.7 Long-Term Persistence/Compliance

For a product to control cholesterol, consumers must take it on a regular, ideally daily basis in order to achieve potential health benefits. Therefore, one of the important objectives of the nonprescription lovastatin development program was to determine the level of persistence and compliance in consumers who self-selected to use the product.

Not all of the clinical use trials in the development program are suitable for determining long-term persistence and compliance in an OTC setting. The design of Study 081 and its extension protocol was inappropriate for assessment of persistence because the total duration was only 3 months, and patients completing the 1 month study were restricted by protocol from entering the extension trial unless they met all label eligibility criteria. Likewise, in Study 079 protocol-specific circumstances regarding the timing and conduct of the study interfered with the return of participants to the final visit and entry into the extension study. Thus, it is inappropriate to draw conclusions about adherence to chronic therapy from Studies 079 and 081.

Two of the nonprescription lovastatin use trials summarized in this application were of sufficient design and duration to gain some insight into consumers' persistence and compliance behavior in an OTC environment. The Pharmacy Study (Protocol 076) evaluated the use of lovastatin 10 mg over a 6-month period, and allowed participants to

enter two 6-month extensions for a total observation period of 18 months. The CUSTOM Study (Protocol 084) evaluated the use of lovastatin 20 mg over a 6-month period. Both studies utilized tablet counts to assess compliance with dosing directions (one tablet per day) instead of daily diary records, since a daily diary might have provided an artificial compliance-enhancing effect. In addition to evaluating persistence and compliance behavior, these studies used data on the percent reduction in LDL-C from baseline as an objective measure to estimate overall compliance with regular dosing. The results from these studies are summarized below.

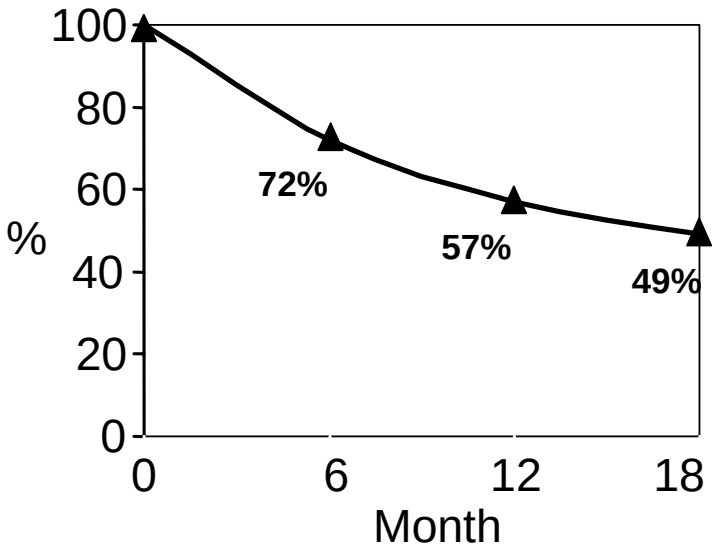
3.7.1 Pharmacy Study (Protocol 076 and Extensions)

Persistence

Persistence with study drug therapy was assessed in all 722 participants who were initially dispensed study drug (lovastatin 10 mg). Persistence was defined as the number of participants who remained in the study at each 6-month interval. This approach is consistent with that used in the CUSTOM study. Figure G-6 shows that, of the 722 participants who were initially dispensed study drug, 72% remained in the study at 6 months, 57% remained in the study at 12 months, and 49% remained in the study at 18 months.

Figure G-6

Pharmacy Study—Long-Term Persistence on Treatment
Percent Remaining in Trial



The Pharmacy Study was initiated with a treatment duration of 6 months; however, interested participants were subsequently given the opportunity to extend their treatment for 2 additional 6-month periods, for a maximum treatment duration of 18 months. Because this was not a continuous 18-month study, participants had to "re-enroll" (sign a consent form addendum) for each treatment extension (once at 6 months, and again at 12 months). Therefore, the potential existed that some participants would not continue into a treatment extension simply because they were unwilling to continue since they did not know from the beginning that the study would be 18 months. For this reason, the persistence within each 6-month extension was also evaluated. Data from this evaluation demonstrated that, of the 465 participants who completed the original 6-month period and enrolled in the first 6-month extension, 414 (89.0%) completed 12 months of treatment, and of the 389 participants who entered the second 6-month extension, 357 (91.8%) completed 18 months of treatment. Overall, 76.7% (357 of 465) of the participants who continued in the study at 6 months remained in the study through 18 months. These data indicate that individuals who are motivated to remain on therapy at the end of 6 months are highly likely to continue on therapy through 18 months.

Compliance

Compliance with dosing directions in the Pharmacy Study was measured only in the participants who were considered persistent at the end of each 6-month period, and was expressed as the number of tablets consumed divided by time in study during a 6-month interval. Participants were considered compliant if, during a 6-month period, they consumed at least 75% of the tablets dispensed in that period.

The participants who remained on treatment exhibited a high degree of compliance throughout the 18-month study. For each of the time intervals (1 to 6 months, 7 to 12 months, 13 to 18 months) more than 80% of participants took at least 75% of their medication. The compliance results (based on tablet counts) were compared to the objective measure of mean LDL-C reduction at the end of each 6-month interval. Mean LDL-C reductions for 10 mg of lovastatin were 23.9%, 20.2%, and 22.8% at the end of 6 months, 12 months, and 18 months, respectively. These results confirm the good compliance observed from tablet counts.

3.7.2 CUSTOM Study (Protocol 084)

Persistence

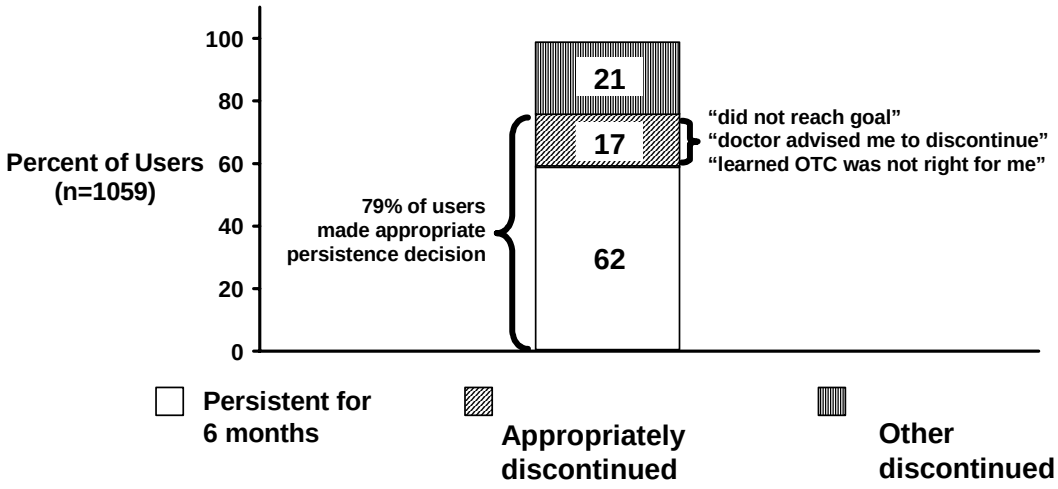
Persistence with study drug therapy (lovastatin 20 mg) was assessed by determining the number (%) of Users who remained in the study for >24 weeks (168 days). Users were defined as participants who took at least one dose of study drug. Of the 1061 Users, 61.8% (656/1061) had a treatment duration of at least 169 days, and are considered persistent for 6 months.

It is important to note that the MEVACOR™ OTC Self-Management System contained prominent and pervasive messages encouraging appropriate discontinuation of therapy if a Purchaser was: ineligible but self-selected to use, if goal was not reached, if unexplained muscle pain developed, or if directed by their personal physician (potential underestimate of persistence). Of the 405 Users who did not persist with treatment for 6 months, 178 discontinued because of the above messages encouraging appropriate discontinuation. Therefore, as illustrated in Figure G-7, if these Users are combined with the 656 who persisted, a total of 79% of Users (656+178/1061) made an appropriate persistence decision.

Related information on persistence in CUSTOM was provided in the Post-CUSTOM Survey. Of the 398 Users who responded to the survey, 266 reported that they generally used MEVACOR™ OTC throughout the 6-month study period. When these 266 individuals were asked about the likelihood of their continuing with MEVACOR™ OTC had it been available after the study, 77% (205/266) responded that they would have been "very likely" to continue to use the product, and another 9% (25/266) said they would have been "somewhat likely" to continue use. These data suggest that most people who use MEVACOR™ OTC for the first 6 months would continue to use the product over the long term.

Figure G-7

CUSTOM: Persistence at 6 Months



Compliance

Compliance was calculated as the number of tablets taken divided by the number of days Users had access to medication. Compliance of 1 (100%) would imply a dosage of 1 tablet per day. The population evaluated for compliance was all 1059 Users. The percent compliance can be more than 100% for several reasons, including:

- User actually took more than 1 tablet per day
- Artifacts created by data handling and entry guidelines
- Error in data collection or entry (discovered after database lock)

Six Users who had a calculated compliance of more than 200% were considered outliers, and were not included in the evaluation of compliance. Explanations are provided below:

- In 4 cases, compliance was more than 200% because of an error in data entry which was discovered after database lock.
- One User discontinued therapy after 13 days due to a clinical adverse experience, but returned 0 of the 45 tablets dispensed.
- One User took 2 tablets per day (180 tablets total) without being directed to do so by a physician.

The percentage of Users who were between 75% and 120% compliant was 56%. There were very few Users with more than 120% compliance (i.e., took more than one additional tablet on average for every 5 days of therapy). Not counting the 6 outliers noted above, only 22 Users had more than 120% compliance. Therefore, although the study design did not permit assessment of the degree to which an individual User may have exceeded once-daily dosing instructions on any given day, the data available support the conclusion that there is no evidence of excessive dosing on a chronic basis in the User population.

Overall compliance was also estimated using the objective measure of percent LDL-C reduction from baseline to end of study. The rationale is that a meaningful percent reduction in LDL-C is a surrogate marker for compliance with dosing directions. The median percent reduction in LDL-C was 20.6% in all Users with a baseline and end-of-study LDL-C value. This calculation did not account for fasting status or Users who discontinued therapy long before returning for the final visit (a median LDL-C reduction of 25.2% was observed in the cohort of 243 Users who fasted at baseline and end of study). These results suggest that there was good overall compliance with dosing directions over the duration of the CUSTOM study.

3.7.3 Comparison With Persistence Data From Prescription Experience

In order to compare the results from the CUSTOM Study and the Pharmacy Study with data from prescription experience, it is important to understand how the unique design features of these studies potentially impact the evaluation of persistence, and what prescription study data are most appropriate for comparison. Some of the study design features are noted below, along with their potential effect on evaluation of persistence:

CUSTOM Study and Pharmacy Study

- The reach of mass media advertising was sometimes quite far from the study locations, and some participants were inconvenienced by having to travel long distances to reach the study sites (potential underestimate of persistence).

CUSTOM Study

- The MEVACOR™ OTC Self-Management System contained prominent and pervasive messages encouraging appropriate discontinuation of therapy if a Purchaser was: ineligible but self-selected to use, if goal was not reached, if unexplained muscle pain developed, or if directed by their personal physician (potential underestimate of persistence).
- Because of the minimally intrusive data collection process, study drug therapy stop date was not collected from Users. Instead, the date of last drug return (or last contact with the User if drug was not returned) was used as a surrogate for therapy stop date (potential overestimate of persistence).
- From data collection worksheet comments it was apparent that some Users "remained in the trial" until their scheduled last visit even if they had discontinued study drug long before their final visit, or had never taken any drug (potential overestimate of persistence)
- The assessment of compliance was impacted by some of the same issues noted for persistence (e.g., compliance would be underestimated in Users who returned for their final visit long after they discontinued therapy).

Pharmacy Study

- Participants did not have to purchase the study medication (could either potentially overestimate or underestimate persistence).
- Only participants who were eligible per product label criteria were permitted to receive study drug (potential overestimate of persistence).
- Participants received no guidance or encouragement from the health care professional (pharmacist) at what would have been the point of purchase in a nonprescription marketplace (potential underestimate of persistence).
- The study was not originally designed as an 18-month study, but was a 6-month study with two subsequent 6-month extensions, a design anomaly which may have affected participants' decisions to continue (potential underestimate of persistence).

Since the above issues are unique to these consumer behavior studies, the persistence results must be interpreted with caution when comparisons are made to data from chronic use of prescription drugs. Specifically, comparison to results from traditional double-blind, placebo-controlled clinical trials conducted in a clinic setting is inappropriate for several reasons. Typically, these studies are designed to evaluate therapeutic efficacy of the drug product, and good persistence and compliance with therapy is necessary for a valid assessment of efficacy. Patients who are unlikely to be persistent are often screened out through such mechanisms as placebo run-in phases. In addition, patients are closely monitored through scheduled visits, and may receive behavioral reinforcement from study personnel. Daily diaries or electronic medication monitoring devices may be used to maximize and track persistence and compliance. The resultant persistence and compliance data from such trials represent an idealized environment that is not representative of either a primary care setting or an OTC setting.

The most appropriate comparisons are against results from community-based studies; therefore, the persistence and compliance data from the CUSTOM Study and the Pharmacy Study were compared with data from the prescription drug setting, including administrative databases, managed care databases, and community pharmacies [140; 141; 142; 143]. Specifically, Jackevicius et al. [142], using an administrative database from Ontario, Canada, found that elderly patient adherence rates to statins at two years (defined as a statin being dispensed at least every 120 days after the index prescription at 2 years) was only 25% for primary prevention users. Data from both the New Jersey Medicaid and Pharmaceutical Assistance to the Aged and Disabled programs was evaluated for the determination of statin use among elderly patients [140; 141]. Full adherence to statin therapy (defined as patients with a proportion of days covered of 80% or higher in a given interval) was 60%, 43%, 26%, and 32% after 3, 6, 60, and 120 months, respectively. Nonadherence to statin therapy (defined as those with a proportion of covered days <20%) increased rapidly to 29% at 6 months and 56% at 60 months.

Recent data from the World Health Organization (WHO) studying patient behavior in developed countries demonstrates that fewer than 50% of patients follow their doctor's directions for taking drugs prescribed for chronic conditions [144]. Adherence to such long-term therapy was defined by the WHO study as "the extent to which a person's behavior (taking medication, following a diet, and/or executing lifestyle changes) corresponds with agreed recommendations from a health care provider." Adherence, as defined by WHO, was at least as good in CUSTOM as the WHO-reported standard of care associated with the involvement of a physician.

The persistence results from the Pharmacy Study at 12 months were compared with two published studies that evaluated persistence with lovastatin over a 1-year period by analyzing prescription refill records. The 64 [145] to 50% [146] of participants who persisted on therapy at 1 year in those studies was very consistent with the 57% persistence rate observed in this Actual Use study situation.

The conclusion from all of the above comparisons is that the long-term persistence and compliance data from nonprescription use of lovastatin 10 mg or 20 mg compares favorably with published data for chronic prescription physician-directed therapy with statins.

3.7.4 Summary of Long-Term Persistence and Compliance Results

The CUSTOM Study provides information on persistence and compliance in a general User population that includes individuals who are ineligible for nonprescription lovastatin according to label criteria, and who may be influenced by the MEVACOR™ OTC Self-Management System to appropriately discontinue. The Pharmacy Study provides longer term data on persistence and compliance in the subset of the User population that met label eligibility criteria. Together, data from both studies provide meaningful insight into consumer behavior regarding persistence and compliance with lovastatin therapy in a nonprescription environment.

Results from the CUSTOM and Pharmacy Studies demonstrate the following:

- Long-term persistence and compliance with lovastatin in a nonprescription setting compares favorably with published literature on experience with prescription statins.
- There is no evidence of excessive dosing on a chronic basis
- A substantial proportion of individuals who begin to use nonprescription lovastatin will persist with therapy over the long-term, will comply with daily dosing directions, and may thereby obtain substantial cholesterol reduction, with potential reduction in overall CHD risk.

4. Summary of Consumer Behavior

An important question in determining whether a cholesterol-lowering medication is appropriate for nonprescription treatment is whether people can appropriately self-select treatment without the direct involvement of a physician. The second important question regarding consumer behavior is whether they will use the product appropriately once the selection is made. Data from the CUSTOM Study and the nonprescription lovastatin 10 mg Actual Use studies provide substantial evidence in support of an affirmative answer to both of these questions.

The clinical Actual Use studies have shown that there are a variety of ways to assist consumers in the decision process. Pharmacy personnel in locations with functioning community-based retail pharmacies can be trained to obtain the fingerstick lipid profiles and to guide the decision process appropriately should they be asked to do so by consumers in the marketplace. Non-medical trained product specialists can also effectively support the self-selection process through a toll-free telephone service.

Given the multi-factorial approach proposed for MEVACOR™ OTC, it should come as no surprise that a substantial number of Users in CUSTOM did not meet all of the specific label eligibility criteria relating to benefit (although many consulted a physician, which technically meets label requirements). For this reason, some may interpret the outcome of the CUSTOM study as relatively negative if assessed rigorously in terms of pure label compliance. However, 100% adherence to each aspect of the selection criteria is not critical to appropriate self-selection in this indication of lipid lowering and CHD risk reduction. This more global approach to interpreting behavior is in contrast to traditional OTC product indications for symptomatic conditions or safety warnings, where each message/criterion is often independently important. Indeed, in CUSTOM there was a high level of adherence to the label safety criteria.

Similarly, many of the Users in CUSTOM would be estimated to be outside of the 10% to 20% 10-year risk ATP III target and ideally would not be prospectively targeted to use MEVACOR™ OTC. However, analysis of this population suggests a substantial health benefit would be achieved despite the somewhat lower or higher average absolute risk (see E. Brass analysis in Appendix F). Thus, the label meets its objectives. While not meeting a high "heeding standard" in the traditional sense, it represents an appropriate and validated OTC label through use of surrogates to reach the intended target population.

The data from CUSTOM demonstrate that the MEVACOR™ OTC Self-Management System enables self-selection, appropriate de-selection, and self-management of elevated cholesterol by consumers in accordance with the ATP III recommended LDL-C goal and guidelines. As such, it represents an important option in an overall "stepped care" approach to CHD risk management. The CUSTOM study demonstrated that consumers at varying levels of risk for CHD benefit from the MEVACOR™ OTC Self-Management System. By and large, the targeted population of intermediate risk consumers is able to appropriately choose to use MEVACOR™ OTC, and readily partner with their physicians to achieve maximal benefit from drug therapy. Moreover, the overall potential for safety concerns is minimal for consumers using the MEVACOR™ OTC Self-Management System. CUSTOM also demonstrated that consumers using lovastatin 20 mg in an OTC environment can achieve LDL-C lowering and treatment-to-goal at rates similar to established medical care benchmarks, and that lovastatin 20 mg is well-tolerated, with an adverse experience profile similar to that observed in randomized, controlled trials (See Sections C. Efficacy and Benefit of Lovastatin and E. Safety of Lovastatin of this Background document for more details of lovastatin 20 mg efficacy and safety results from CUSTOM).

5. Consumer Behavior Conclusions

Successful consumer self-selection of nonprescription treatment can be achieved by optimizing the presentation of key messages in product promotion, and on the carton label, including effective label reinforcement and educational tools within the carton. Maximizing marketplace incentives to consult the product specialist through toll-free phone or website access is also an important goal. Communication with physicians as partners in the self-medication program can be encouraged and facilitated in the marketplace. Establishment of the habit of regular daily dosing can also be facilitated by compliance support programs and incentives. Consumers have demonstrated their awareness, willingness, and ability, with appropriate support, to commit to self-treatment with a cholesterol-lowering medication to maintain their health.

Conclusions:

- Consumers interested in a nonprescription cholesterol-lowering product are aware of cholesterol as a health risk factor.
- Product advertising and labeling are effective at directing consumers to know their lipid values before making a product purchase decision, or to consult with a physician before beginning to use nonprescription lovastatin.
- Consumers' knowledge of LDL-C and Total-C is sufficiently accurate to support appropriate purchase and use decisions.
- The product labeling and reinforcement tools inherent in the MEVACOR™ OTC Self-Management System (including the package circular, educational information, and toll-free call support line to product specialists) effectively guide consumers toward appropriate self-selection and continued use of nonprescription lovastatin 20 mg.
- Consumers selecting to self-medicate with the product comply well with regular dosing, and a substantial subset will persist on long-term treatment.
- Consumers achieve beneficial lipid lowering which is comparable to that observed in controlled clinical trials.
- MEVACOR™ OTC is generally well tolerated when used in an OTC setting, with an adverse experience profile similar to that observed in controlled clinical trials.
- Therapeutic lifestyle patterns (such as diet and exercise) are encouraged and maintained or improved with the MEVACOR™ OTC Self-Management System.
- The MEVACOR™ OTC Self-Management System encourages healthcare professional interactions for both users and non-users of the product.

H. SUMMARY OF OVERALL BENEFIT OF OTC ACCESS TO LOVASTATIN 20 MG

1. Introduction

This background package supports the proposal for nonprescription availability of over-the-counter (OTC) MEVACOR™ (lovastatin) 20 mg for the reduction of moderately elevated LDL-C (130-170 mg/dL) in otherwise healthy individuals at intermediate risk for coronary heart disease (CHD). MEVACOR™ OTC will serve as an adjunct to therapeutic lifestyle changes including weight loss, diet, and exercise. In an NDA for a prescription drug, 2 key questions are "How well does the drug treat the condition at the proposed dose?" and "Are the potential safety risks worth the benefits of treatment?" In this package, these 2 questions are appropriately considered in the context of a third question: "How well do people self-manage this condition without direct supervision of a physician?"

Differences between this proposal and the traditional OTC switch criteria include the following:

- the condition being treated is asymptomatic and requires the ancillary measure of lipid testing to self-diagnose and determine the adequacy of drug treatment
- the consumer is required to interpret his/her lipid profiles using guidance provided by the labeling
- the benefits of treatment require long-term use

In addition, individuals at higher cardiovascular (CV) risk may be relatively under-treated by such an OTC drug without more comprehensive medical care and individuals at lower CV risk may expose themselves to a chronic medication unnecessarily. Noncompliance with therapy, whether prescription or OTC, may result in failure to achieve benefit. Each of these components is discussed in detail in the following sections.

The benefits of providing nonprescription access to lovastatin 20 mg to lower cholesterol can be justified for the following reasons:

1. The efficacy of MEVACOR™ with respect to both lipid lowering and coronary heart disease (CHD) risk reduction at the proposed 20-mg dose is substantial and well-established for the recommended OTC population.
2. The extensive use of prescription doses up to 4 times greater than the 20-mg dose provides abundant information on the excellent general safety of the product.
3. The primary prevention intermediate risk population is now indicated for an effective and safe cholesterol reducer to improve CV health. This need is not being met (referred to as the cholesterol treatment gap) in the current prescription environment.

4. Important public health benefits could result from lowering cholesterol levels in the target population.
5. The MEVACOR™ OTC Self-Management System (MOTC-SMS) has been demonstrated to direct appropriate self-selection and self-administration of MEVACOR™ OTC.
6. The MOTC-SMS encourages and promotes consumer interactions with healthcare professionals leading to greater awareness and management of CHD risk.

This section of the Background document will review data that demonstrate how the potential challenges associated with product use can be overcome, and clearly show that the potential benefits outweigh the potential treatment risks. This section will also take into account both individual and population perspectives in those defined as OTC statin-eligible and will also address inappropriate use of the product by those with a CV risk higher or lower than that of the targeted intermediate risk population. The assessment of benefit versus risk will also consider inappropriate usage of the product, despite clearly stated label directions and warnings.

2. Potential Benefits of Nonprescription Lovastatin 20 mg

The OTC statin-eligible population is a *primary prevention* population with an intermediate risk of coronary heart disease (CHD) over 10 years. According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), commonly referred to as ATP III, the intermediate risk population [23] is eligible for lipid-lowering therapy and consists of individuals with 2 or more CHD risk factors whose 10-year risk of a CHD event is ≤20% (by the Framingham Risk Scoring Measure [22]). ATP III has recommended a low density lipoprotein cholesterol (LDL-C) target goal of <130 mg/dL for this population. Using data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994) and Year 2000 U.S. population information, Ford et al. estimate that the year 2000 U.S. population (Age 20 to 79 years) includes 23 million individuals without CHD or a CHD equivalent *and* who have 10-year risk for developing CHD in the 10% to 20% range [12]. While this population estimate does include some "lower risk" individuals with less than 2 CHD risk factors, it does not include OTC statin-eligible persons who have 10-year CHD risk <10% but who have 2 or more CHD risk factors. Fedder et al. have also used NHANES III to determine that 36 million U.S. adults (ages 20 to 79 years) are eligible for primary prevention drug therapy under ATP III [30]. While it is true that the 36 million estimate includes some "higher risk" individuals (diabetics and persons with 10-year risk for developing CHD exceeding 20%), it is likely that the OTC statin-eligible population in the U.S. falls somewhere in between these 2 estimates (i.e., 23 to 36 million individuals). Despite ATP III guidelines, only 37% of the intermediate risk population is on lipid-lowering therapy [32]. Furthermore, since 1993, notwithstanding a multitude of advances in the treatment and understanding of CHD, the cholesterol treatment gap for the intermediate risk population has remained unchanged [147].

The OTC Statin-Eligible Population excludes patients who are pregnant, breast-feeding, have current liver disease, or are allergic to a statin. Medical consultation is recommended for individuals on therapy with other prescription drugs and those with LDL-C >170 mg/dL, high triglycerides (a surrogate for the metabolic syndrome), diabetes mellitus, CHD, or history of stroke before considering OTC statin therapy.

3. Estimation of CV Risk and Risk Reduction in the OTC Statin-Eligible Population

By definition, the OTC Statin-Eligible Population has an intermediate risk for developing CHD. The effects of lovastatin 20 to 40 mg on this risk group was evaluated in The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). This 5.2-year, randomized, double-blind, placebo-controlled study evaluated 6605 individuals with average total cholesterol and LDL-C, but below-average HDL-C. Seventy-five percent (75%) of the participants in AFCAPS/TexCAPS were at intermediate risk for CHD by ATP III guidelines [22; 23]. The observed event rate for the placebo-treated group (N=3301) in AFCAPS/TexCAPS was 5.6 events (fatal and nonfatal myocardial infarction) per 1000 patient-treatment years (comparable to a 10-year CHD risk of 5.6%). Therapy with lovastatin (20 to 40 mg daily) resulted in a reduction in the incidence of first acute major coronary events (183 versus 116 first events on placebo versus lovastatin, respectively; relative risk [RR] 0.63; 95% confidence interval [CI], 0.50 to 0.79; P<0.001), myocardial infarction (95 versus 57 myocardial infarctions; RR, 0.60; 95% CI, 0.43 to 0.83; P=0.002), unstable angina (87 versus 60 first unstable angina events; RR, 0.68; 95% CI, 0.49 to 0.95; P=0.02), coronary revascularization procedures (157 versus 106 procedures; RR, 0.67; 95% CI, 0.52 to 0.85; P=0.001), coronary events (215 versus 163 coronary events; RR, 0.75; 95% CI, 0.61 to 0.92; P=0.006), and cardiovascular events (255 versus 194 cardiovascular events; RR, 0.75; 95% CI, 0.62 to 0.91; P=0.003). Lovastatin (20 to 40 mg daily) reduced LDL-C by 25% to 2.96 mmol/L (115 mg/dL) and increased HDL-C by 6% to 1.02 mmol/L (39 mg/dL) [7].

Kaplan-Meier estimates from the entire AFCAPS/TexCAPS study population (N=6,605) indicate that one would need to treat 34 individuals for 6 years in order to prevent a first acute CHD event (fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death). A significant subset of the AFCAPS/TexCAPS study population met the MEVACOR™ OTC label eligibility criteria (N=2,882, 43.6%). Kaplan-Meier estimates from this subgroup indicate that one would need to treat 25 individuals for 6 years in order to prevent a first acute CHD event.

Of this MEVACOR™ OTC eligible subset of the AFCAPS/TexCAPS study population, 775 of the 1,433 participants who were randomized to the lovastatin treatment group remained on 20 mg/day for the duration of the trial (non-titrators who achieved the study goal of LDL-C<110 mg/dL by Week 18). Compared with a matched placebo group (n=775), there was a 53% reduction in first acute CHD events (fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) in this subgroup

(48 versus 23 events; RR, 0.471; 95% CI, 0.286 to 0.774; p=0.003). Kaplan-Meier estimates from this MEVACOR™ OTC eligible non-titrator subgroup indicate that one would need to treat 16 individuals for 6 years in order to prevent a first acute CHD event. These values must be interpreted with caution due to the limitations of the subset analysis performed and the lack of randomized placebo group. Nonetheless, it is apparent that the benefit of CHD risk reduction observed in the entire AFCAPS/TexCAPS study population is also seen in both the MEVACOR™ OTC eligible subgroup and the MEVACOR™ OTC eligible non-titrator subgroup.

Using the most conservative number needed to treat (NNT=34) from the above analyses, 294 CHD events would be avoided for every 10,000 people having a CHD risk similar to those participating in AFCAPS/TexCAPS treated and self-treating with lovastatin 20 mg/day for 6 years. Although there are some limitations to applying this calculation to the OTC target population, similar benefit would be expected.

An additional population likely to use nonprescription lovastatin, despite the instructions on the proposed label, comprises individuals at lower CHD risk (i.e., those with ≤1 CHD risk factor and a 10-year risk <10%). An analysis was performed on participants in AFCAPS/TexCAPS to determine the CHD event rate for the primary outcome among subpopulations based on the ATP III guidelines. Across subsets, CHD event rates were consistently lower in groups treated with lovastatin compared with similar groups on placebo. The relative risk reduction was 39% (RR 0.61; 95% CI 0.47 to 0.79) among participants eligible for statin therapy by ATP III and 34% (RR 0.66; 95% CI 0.40 to 1.09) among participants not recommended for such therapy by ATP III. The event rate reduction in the subpopulation not recommended for lipid-lowering therapy by ATP III did not achieve statistical significance due to insufficient sample size; there were simply too few events (39 on placebo versus 25 on lovastatin) in this lower risk population. Thus, even lower risk populations not currently recommended for lipid-lowering therapy by ATP III can obtain benefit from lovastatin.

4. Achieving the Benefit of Nonprescription Lovastatin 20 mg in the OTC Environment

The MEVACOR™ OTC Self-Management System (MOTC-SMS) has been designed to be consistent with guidelines established in May-2001 by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [22](updated recommendations released in Jul-2004 [31]). ATP III recommends expanded use of cholesterol-lowering medications in the primary prevention of CHD. Results of key prevention trials such as AFCAPS/TexCAPS show that LDL-C lowering drugs reduce risk for major coronary events and coronary death. Additionally, ATP III recommends a multifaceted lifestyle approach to reducing risk for CHD. This approach is designated therapeutic lifestyle changes (TLC). The essential features of TLC include the adoption of healthy life habits (the cornerstone of primary prevention), including avoidance of smoking (including secondhand smoke), weight control, a healthy diet, and an appropriate exercise program. ATP III guidelines identify reduction of LDL-C as the primary goal of therapy for both TLC and drug treatment.

ATP III establishes goals for LDL-C that are dependent upon a patient's 10-year CHD risk status (as assessed by the Framingham Risk Assessment Scoring Measure) [22]. If LDL-C goals are not achieved by TLC, pharmacologic therapy with lipid-lowering agents is recommended. While ATP III maintains attention to intensive treatment of patients with CHD, its major new feature (compared with earlier versions) is a focus on primary prevention in persons with multiple (2 or more) risk factors. The MEVACOR™ OTC Program is also focused on the primary prevention of CHD in persons at intermediate risk, i.e., those with multiple (2 or more) CHD risk factors and a 10-year risk ≤20% [23]. As per ATP III, the CHD risk factors (exclusive of LDL-C) that modify LDL-C goals include: cigarette smoking; hypertension (BP ≥140/90 mm Hg or on antihypertensive therapy); low HDL-C (<40 mg/dL); family history of premature CHD (CHD in a male first-degree relative <55 years and CHD in a female first-degree relative <65 years); and age (men ≥45 years; women ≥55 years)[22].

As discussed earlier in this document, it is estimated that well over 23 million Americans comprise the intermediate risk population in the U.S. and are eligible for therapy with statins. The NCEP ATP III Executive Summary recognizes that primary prevention of CHD offers the greatest opportunity for reducing the burden of CHD in the United States. As recommended by ATP III, the target treatment goal for the intermediate risk group is LDL-C <130 mg/dL. Recent recommendations [31] have also endorsed the option to seek even more aggressive treatment goals in moderately-high and high risk individuals. In accordance with ATP III, health care professionals are asked to use the Framingham Risk Assessment Scoring Measure to quantitate the 10-year risk of primary prevention patients with 2 or more risk factors [22]. By definition, the MEVACOR™ OTC-Eligible Population has multiple (2 or more) risk factors and a ten-year CHD risk of ≤20%.

The CUSTOM Study, developed with guidance from the Agency, was a 6-month consumer behavior study of the MEVACOR™ OTC Self Management System that occurred in a naturalistic, over-the-counter setting. The MEVACOR™ OTC Self-Management System is a comprehensive system of materials, support services, and consumer communications (e.g., website, toll free phone service, direct mailing) designed to ensure correct consumer behavior regarding cholesterol self-management. The target population defined by the CUSTOM label is consistent with ATP III guidelines, and targets consumers without CHD who are at intermediate risk of a CHD event [23]. Individuals with diabetes, CHD, or a history of stroke are not candidates for MEVACOR™ OTC. The treatment selection paradigm that appeared on the CUSTOM label was designed to guide a consumer decision to use the product based on age (men ≥45 years, women ≥55 years), LDL-C value (130 to 170 mg/dL) and the presence of at least one other risk factor (smoking, HDL-C<40 mg/dL, positive family history or high blood pressure). Exclusion criteria included pregnancy, breast-feeding, allergy to lovastatin, and current liver disease. Individuals taking any prescription medication (including other lipid-lowering agents) were instructed by the label to ask their doctor or pharmacist before using MOTC. The CUSTOM label described events that a consumer

should recognize and act upon regarding the continued use of MEVACOR™ OTC and contact with a physician and/or pharmacist. These events included follow-up cholesterol tests, new medical conditions, new prescriptions, and unexplained muscle pain. If treatment goal was not achieved with lovastatin 20 mg daily after six weeks of therapy, the consumer was directed to consult with a physician. The goal of CUSTOM was to evaluate the effect of the MEVACOR™ OTC Self-Management System on the ability of consumers to appropriately self-select and self-manage their elevated LDL-C.

CUSTOM demonstrated that 86% percent of participants evaluating MEVACOR™ OTC and utilizing the MOTC-SMS made appropriate initial use decisions. The majority of Users (i.e., those that purchased and took at least one dose of MEVACOR™ OTC) demonstrated acceptable ongoing use behavior regarding treatment-to-goal, compliance/persistence, and changes in health status. Throughout the 26-week study, 2% of Users demonstrated behavior that created the potential for suboptimal safety. After 26 weeks, median LDL-C was reduced by 25% among those that fasted with 62% of those tested achieving LDL-C target goal (<130 mg/dL).

Physician interactions were common: 42% of Purchasers spoke to their physician before starting drug. Of Non-User Non-Purchasers, 46% reported their intention to talk to their doctor regarding MOTC and 22% reported a physician interaction regarding MOTC before deciding not to purchase. Furthermore, 74% of high risk Users (i.e., those with a history of CHD, stroke, or diabetes mellitus) interacted with a physician. At study end, 89% of Users were on an AHA Step I or II Diet with improved or maintained dietary patterns and exercise habits in 98% and 94% of Users, respectively. At 26 weeks, 61% of Users remained in the study. MOTC was well tolerated with no observable adverse experiences from drug interactions or reported cases of myopathy.

Thus, the MEVACOR™ OTC Self-Management System, as demonstrated by the CUSTOM Study, generally enables self-selection, appropriate de-selection, and self-management of elevated cholesterol by consumers in accordance with the ATP III recommended LDL-C goal and guidelines (and recently updated recommendations [31]. As such, it represents an important option in an overall “stepped care” approach to CHD risk management. The CUSTOM study demonstrated that consumers at varying levels of risk for CHD do benefit from the MEVACOR™ OTC Self-Management System. By and large, the targeted population of intermediate risk consumers is able to choose to use MEVACOR™ OTC and achieve LDL-C lowering and treatment-to-goal at rates similar to established medical care benchmarks, with many readily partnering with their physicians to achieve maximal benefit from drug therapy. Furthermore, both actual safety results and overall potential for safety concerns are acceptable for consumers using the MEVACOR™ OTC Self-Management System without a prescription. To ensure that consumers achieve comparable results in the marketplace, a self-management system consistent with that used in the CUSTOM trial will be implemented post-launch; this comprehensive consumer support system is further described in the OTC Self-Management System and Post-Launch Monitoring Plan.

5. Potential Risks of Nonprescription Lovastatin 20 mg

5.1 Concern About Suboptimal Treatment of Higher Cardiovascular Risk

5.1.1 Populations

The proposed nonprescription MEVACOR™ OTC carton label is designed to exclude patients with high cardiovascular risk by statements clearly indicating that the product should not be taken by persons with a history of coronary heart disease, stroke, or diabetes. In addition, the carton label recommends against usage by persons with an LDL-C >170 mg/dL and serum triglycerides >200 mg/dL. Such hypercholesterolemic/ hypertriglyceridemic individuals will normally require more aggressive lipid-lowering therapy and are advised by the label to consult their physicians. These individuals might also be considered to be at risk for under-treatment by taking nonprescription lovastatin 20 mg. However, it cannot be assumed that all, or even many, of these high risk (i.e., those with history of CHD, stroke, or diabetes) or hyperlipidemic/ hypertriglyceridemic consumers who would erroneously take nonprescription lovastatin instead of consulting a physician would have consulted their physicians if they had not taken the nonprescription product. In addition, there is no certainty that those individuals who might consult their physicians would receive prescription drug therapy since drug treatment in clinical practice has fallen well short of the ATP III recommendations. The cholesterol treatment gap among intermediate risk populations has been estimated to be at least 62% for primary prevention patients with multiple CHD risk factors [32].

In CUSTOM, a small subset of Users (70 of 1,059 Users; 7%) were at high CHD risk (i.e. those with a history of CHD, stroke, or diabetes) and did not consult with a physician before deciding to use MOTC. A low percentage of high risk individuals will also probably not consult with a physician before deciding to use MOTC in the marketplace despite label warnings. However, 46 of these 70 Users were not on prescription lipid-lowering therapy at the time of self-selection, but should have been by ATP III guidelines. In addition, 26 of these 70 high risk Users reported a physician interaction regarding MEVACOR™ OTC later on during the study. In the marketplace, such high risk populations are likely to achieve some reduction in their cardiovascular risk compared with no treatment. While this is less than can be achieved in many high risk consumers with more aggressive lipid-lowering therapy, it is certainly better than the current alternative for many individuals, that is, no pharmacologic treatment at all. For the short term, suboptimal treatment will provide some benefit and the labeling and educational materials will direct many consumers to discuss their treatment with their physician. The nonprescription product could represent an introductory step toward more comprehensive care, or it may serve as stand-alone treatment where no better option is accessible for whatever reason. Since nonprescription lovastatin 20 mg would likely be purchased out-of-pocket, it would not be a desirable choice for most people who are already under standard physician care and who have some coverage for the cost of prescription medication.

Another group of concern involves individuals currently on prescription lipid-lowering agents who decide to substitute MEVACOR™ OTC (20 mg) instead. Fortunately, such "down streaming" behavior was rare in CUSTOM and involved only 11 Users among 609 participants evaluating the drug that were currently on prescription lipid-lowering therapy. It is thus unlikely that this type of behavior will be substantially different in the marketplace.

Among the 1,059 Users in CUSTOM, 95 reported an LDL-C>170 mg/dL and closely adhered to the label benefit criteria for self-selection and 55 had LDL-C>170 and did not adhere to the label benefit criteria for self-selection. These people were strongly motivated to purchase nonprescription lovastatin 20 mg and self-treat. In fact, it may be speculated that, in the absence of an effective nonprescription drug, a substantial portion of this group may resort to less effective and uncontrolled dietary supplement products.

Concerns have been raised by various stakeholders that availability of an OTC statin would allow managed care organizations to shift costs by forcing enrollees already on prescription statins or new patients to transfer therapy to the OTC statin. This concern was examined by an independent Towers Perrin study. This study was conducted with leaders of 18 managed care organizations from 3 payer segments to better understand their perspectives on the role of a low-dose OTC statin for primary prevention of CHD in the intermediate risk population. Findings of the study revealed that payer policies will continue to support access to prescription statins and no change in formulary status is to be expected should an OTC option become available.

For all of the above reasons, it can be logically concluded that inappropriate use of the nonprescription product by those who have higher cardiovascular risk than the nonprescription-eligible population probably represents a net benefit rather than a negative factor in evaluating the suitability of lovastatin 20 mg for nonprescription use.

5.2 Managing Potential Risks of Nonprescription Lovastatin 20 mg Through Labeling

The final proposed nonprescription back panel label addresses drug safety with warnings reflecting contraindications in the prescription label. A copy of the proposed label for MEVACOR™ OTC is in Appendix I. These include a warning not to use the product if allergic to lovastatin or any of its ingredients, or in case of liver disease, or if a woman is pregnant, may become pregnant, or is breast-feeding. Further protection is provided by the label advising use for women aged 55 years or older.

Consumers are directed to ask their doctor or pharmacist before use if taking any prescription medicine, other cholesterol-lowering medicine, or new prescriptions. In addition, if the consumer is diagnosed with any new medical condition, he/she is advised to tell their doctor they are taking MEVACOR™ OTC. Drug discontinuation is advised in the event that the consumer develops any unexplained muscle pain, weakness, or tenderness. These messages are again reinforced in the package insert and other informational material accompanying the product.

The concern about suboptimal treatment of people with higher cardiovascular risk than defined in the OTC-eligible population is addressed first in the "Use" section by defining LDL cholesterol levels appropriate to be treated with this product (130-170 mg/dL) and second in the "Talk to your doctor" warning section. Here it is stated not to take the product except under direction of a doctor in case of LDL-C>170 mg/dL, triglycerides >200 mg/dL, existing CHD, diabetes, or prior history of stroke. Furthermore, individuals with adequate levels of HDL-C (> 60 mg/dL) are advised to talk to their doctor before using MEVACOR™ OTC to avoid any unnecessary usage.

Label comprehension testing of the CUSTOM label showed a high level of comprehension for all of the above important messages (See Appendix G). In addition, label reinforcement tools similar to those included in CUSTOM (e.g., package circular and informational booklet) were shown to further increase comprehension levels in 2 previous label comprehension studies; these tools would also be expected to enhance understanding of the key information in the CUSTOM label.

A consumer's ability to self-select for MEVACOR™ OTC appropriately according to the label inclusion and exclusion criteria was tested in CUSTOM. As summarized in detail in the CUSTOM clinical study report, over the 26-week study period, 2% of Users demonstrated behavior that created the potential for suboptimal safety. At the time of self-selection, 23 Users had the potential for safety concern by initiating therapy with MEVACOR™ OTC without discussing such therapy with their physician (including 3 Users among 80 Evaluators with current liver disease, 10 Users among 152 Evaluators possibly on potentially interacting medications, and 10 Users among 609 Evaluators possibly on concomitant lipid-lowering therapy). During the study, 9 Users had the potential for safety concern by not adhering to the label criteria (including 8 that developed unexplained muscle pain and did not discontinue MEVACOR™ OTC or inform their physician and 1 that developed diabetes mellitus and did not inform his/her physician about MEVACOR™ OTC). Actual safety demonstrated that MEVACOR™ OTC was well tolerated with no observable adverse experiences from drug interactions or reported cases of myopathy. Only one serious drug-related adverse experience occurred: the development de novo of a systemic-type allergic reaction to MEVACOR™ OTC.

The MEVACOR™ OTC Self-Management System also encourages consumers to consult with a healthcare professional regarding cholesterol management. In CUSTOM, 57% of Users stated that they talked to their doctor about MEVACOR™ OTC Self-Management System. In addition, 46% of Non-Purchasers reported that they intended to talk to their doctor regarding cholesterol management and MEVACOR™ OTC. Twenty-two percent (22%) of the Non-Purchasers reported that they did in fact talk to their doctor prior to making a decision to not buy the product. Furthermore, 74% of all high CHD risk Users (i.e., those with a history of diabetes, CHD, or stroke) interacted with their physician at some time during the study.

Thus, the data provided in the application support the conclusion that labeling and label reinforcement tools inherent in the MEVACOR™ OTC Self-Management System reduce important self-selection errors and guide many people who can benefit from treatment into appropriate use of the product. To ensure proper consumer behavior in the marketplace, a self-management system consistent with that used in the CUSTOM trial will be implemented post-launch; this comprehensive consumer support system is further described in the OTC Self-Management System and Post-Launch Monitoring Plan.

5.3 Balance of Potential Benefits and Potential Risks of Nonprescription Lovastatin 20 mg in the OTC-Eligible Population

5.3.1 Benefit to Target Population

The OTC-eligible population includes millions of otherwise healthy Americans who are at risk for coronary heart disease and are not being treated with cholesterol-lowering agents. Despite this treatment gap, consumers are demonstrating a significant unmet demand for treatment by choosing to buy any of a proliferating array of food, vitamin or "nutriceutical" products touted as cholesterol reducers.

The OTC Statin-Eligible Population has an intermediate risk of developing CHD over 10 years. Based on the results of the AFCAPS/TexCAPS study (where 75% of participants were determined by ATP III criteria to be at intermediate risk for CHD), the benefit of treatment with nonprescription lovastatin 20 mg in this group is conservatively estimated to result in 294 events avoided for every 10,000 people treated for 6 years (based on NNT=34). The number of OTC Statin-Eligible individuals needed to treat for 6 years to prevent one CHD event is likely to be similar.

The impact of preventing CHD events is substantial. CHD is the leading cause of death in American men and women. A major CHD event carries a poor prognosis. Approximately 42% of individuals that experience a myocardial infarction (MI) will die from it. Within one year of a myocardial infarction, 25% of men and 38% of women will die. Fifty percent of men and 64% of women who experience sudden death from CHD have no prior symptoms of this disease. Furthermore, 80% of CHD mortality in people under the age of 65 occurs during the first MI. Many others will be disabled with heart failure or suffer other cardiovascular events. Furthermore, CHD is a leading cause of permanent premature disability which causes loss of economic stability, and quality of life to the individual, and loss of productivity in our society. The economic burden of CHD is considerable (approximately $133.2 billion for 2004), including the cost of hospitalizations, cardiac catheterization, and coronary artery bypass surgery [3].

5.3.2 Indirect Benefits of OTC Access

Direct access to lovastatin 20 mg without a prescription will have beneficial effects in other regards as well. The availability of the nonprescription product with the SMS, in conjunction with responsible consumer advertising, will expand consumer awareness of cholesterol as an important cardiovascular risk factor. As demonstrated by the CUSTOM study, many Non-Purchasers will interact with their physician to discuss their cholesterol concerns and individuals using MEVACOR™ OTC who had never discussed cholesterol with their physician or had not done so for more than 2 years (92 of 269) will engage in such a discussion. Furthermore, CUSTOM demonstrated that users of MEVACOR™ OTC will maintain or improve therapeutic lifestyle patterns including diet and exercise. Consumer product advertising is more effective than direct to consumer prescription advertising in driving home the message, precisely because the product, with its informative labeling, is accessible on the store shelves. A responsive consumer who is self-motivated to initiate treatment may also be more committed to comply with therapy than someone who is passively treated by their physician. In addition, the convenience of obtaining a product at retail pharmacy locations is also conducive to starting and maintaining treatment.

Along with the OTC-eligible population, the high cholesterol and high CHD risk populations will be exposed to information about cholesterol and CHD. While the label directs these individuals to a physician for optimal cholesterol management, some will heed the advice but others will proceed to take the nonprescription product anyway. For some, the nonprescription product may represent the only accessible option, which will give them some benefit. For others, it may serve as an introductory step to comprehensive medical management. The net effect, even for the ineligible population, is likely, therefore, to be positive. As demonstrated in CUSTOM, 74% of high risk users (i.e., those with a history of diabetes, CHD, or stroke) did interact with their physician and discuss statin therapy as a direct consequence of using MEVACOR™ OTC.

5.3.3 Potential for Myopathy

A significant component of the risk side of the benefit-risk equation with lovastatin is the rare and usually reversible occurrence of myopathy. Safety data show that lovastatin is well tolerated in doses up to 80 mg. Muscle toxicity is rare with a dose-response relationship. Very few cases of rhabdomyolysis or death are known with the 20-mg dose despite 27 million patient-treatment years of exposure. The risk of myopathy at the 20-mg dose is expected to be less than the incidence observed in EXCEL of 3 cases per 10,000 treated with lovastatin 40 mg/day over 48 weeks [135]. Since myopathy usually appears within a few weeks of starting treatment, but can occasionally appear later, the incidence with the 20-mg dose over a 5-year period would not be expected to be greater than 5 times higher than the 1-year incidence. Nevertheless, the low potential for

myopathy with lovastatin 20 mg exists even without concomitant medications, as with any other HMG CoA reductase inhibitor. Such an occurrence, however, would most likely be of the milder form, and a very rare event. While the risk of myopathy to an individual would be increased in frequency and severity with concomitant use of interacting drugs, the risk would remain very low. It is reassuring that in the AFCAPS/TexCAPS study, concomitant use of lovastatin and strong CYP3A4 inhibitors was not associated with increased frequencies of muscle-related adverse experiences compared with placebo. There were no cases of myopathy or rhabdomyolysis among these patients.

An important goal of the nonprescription label is to discourage consumers from inappropriate use of nonprescription lovastatin 20 mg with concomitant medications that can interact adversely. The proposed label specifically advises consumers to ask their doctor or pharmacist before beginning treatment with MEVACOR™ OTC if he/she is taking or prescribed *any* prescription medication or other cholesterol lowering medication. Furthermore, the consumer is advised to notify his doctor if he is already on MEVACOR™ OTC and develops an emergent medical condition or before beginning any *new* prescription medication. These advisory statements were very well understood by consumers in both label comprehension testing (See Appendix G) and acted upon in the CUSTOM study.

5.3.4 Comparison to OTC Low-Dose Aspirin

A useful comparison when considering the benefit-risk relationship for lovastatin 20 mg is that for low-dose aspirin (usually defined as ≤325 mg/day). The widespread use of low-dose aspirin is facilitated by its OTC status, with associated public health benefits [148]. Over 23% of the U.S. population use nonprescription low dose aspirin [27]. The majority use low-dose aspirin for cardioprotection, often initiated on the advice of their physician and continued on a long-term basis. According to the most recent recommendations by the U.S. Preventive Health Service for low-dose aspirin use in the primary prevention of CHD, low-dose aspirin is warranted when the risks for a cardiovascular event outweigh the risks for NSAID gastropathy [149; 150]. This threshold is reached at the 3% 5-year risk for CHD events. The population indicated for OTC low-dose aspirin is at *lower* risk for a CHD event (≥0.6 % per year) than the OTC Statin-Eligible Population (10 to 20% 10-year risk or 1.05% to 2.21% per year). Therefore, based on the guidelines of the US Preventive Health Service, the OTC Statin-Eligible Population is also considered to be appropriate for therapy with low-dose aspirin.

It is of interest to examine the benefit/risk relationship of low dose aspirin as it relates to that of an OTC Statin. However, there is attendant risk with chronic use of low-dose aspirin. The risk of NSAID gastropathy from prophylactic low-dose aspirin, as determined by hospital admission for peptic ulcer bleeding is dose-related [151]. Aspirin for primary prevention significantly increases the risk of major bleeding complications by 69% [152]. For 10,000 patients with a 5% risk for CHD events over 5 years (i.e., a 9.5% risk over 10 years), aspirin would cause 0 to 20 hemorrhagic strokes and 20 to 40 major

gastrointestinal bleeding events over that 5-year time period [149]. Table H-1 displays the serious adverse event rates from low-dose aspirin are considerably higher than the adverse event rate of greatest concern with statin therapy, rhabdomyolysis, which occurred at a rate of 0.03% (3 per 10,000) with lovastatin in the large placebo-controlled AFCAPS/TexCAPS trial over an average 5.2 years [7].

Table H-1

Estimated Incidence of Serious Adverse Experiences of Greatest Concern
While Taking
Low-Dose Aspirin or Lovastatin Compared With 5-Year NNT to Prevent CHD Event

	Low Dose Aspirin		Lovastatin 20-40 mg	
Adverse experiences per 10,000 people (over ~5 years)	GI bleeding	20-40[†]	Rhabdomyolysis	3[‡]
	Hemorrhagic stroke	0-20[†]		
Five year NNT	~70[§]		~50[‖]	

[†] Based on 2 to 4 episodes of gastrointestinal bleeding and 0 to 2 events of hemorrhagic stroke in 1000 middle-aged persons given aspirin for 5 years [149].

[‡] Based on 1 reported case of rhabdomyolysis in the 3304 patients treated with lovastatin in the AFCAPS/TexCAPS trial.

[§] Calculated from [149]. Assumes: 5% baseline risk of CHD over 5 years, 14 CHD events avoided for every 1000 patients receiving aspirin for 5 years, and a relative risk reduction of 28%. CHD events include nonfatal acute MI and fatal CHD.

[‖] Based on 3304 patients treated with lovastatin in the AFCAPS/TexCAPS trial for ~5 years; CHD events include nonfatal or fatal MI, unstable angina, or sudden cardiac death as first event [47].

NNT = Number needed to treat.
CHD = Coronary heart disease.
AFCAPS/TexCAPS = The Air Force/Texas Coronary Atherosclerosis Prevention Study.
MI = Myocardial infarction.

[149; 47]

Furthermore, the benefit of low-dose aspirin for primary prevention has been estimated to be a relative risk reduction of approximately 28% for CHD events (nonfatal acute MI and fatal CHD) based on a meta-analysis of 5 large trials [149]. For patients with a 5-year CHD risk of 5 %, treatment with low-dose aspirin would prevent 14 CHD events over 5 years, corresponding to an NNT of ~70. In comparison, approximately 50 patients would need to be treated with lovastatin for 5 years to prevent 1 CHD event [47]. Thus, the benefit from low-dose aspirin is thus similar to (or even less than) the overall benefit reported with statins (and specifically lovastatin) for primary prevention. The long-standing acceptance of low-dose aspirin for OTC use in the primary prevention of CHD illustrates how a commonly used OTC drug taken on a chronic basis can benefit the population and have an acceptable risk profile. Although the FDA Cardiovascular and Renal Drugs Advisory Committee (Dec-8-2003) has not yet endorsed professional labeling for low-dose aspirin in primary prevention, primary prevention continues to be actively promoted in the OTC marketplace and aspirin is often recommended by physicians for that indication.

6. Summary of Benefit Versus Risk of Nonprescription Lovastatin 20 mg

The balance of benefit to risk of treating the OTC-eligible population with MEVACOR™ OTC can be stated quantitatively. For every 10,000 people treated over 6 years, 294 CHD events could be avoided and very few cases, if any, of myopathy would occur. Also, a CHD event is generally far worse than myopathy, as an outcome.

Survey and label comprehension data show that the majority of individuals who are interested in purchasing nonprescription lovastatin understand cholesterol as a risk factor and the need for lipid testing. In addition, actual use studies demonstrate that many are compliant with dosing for up to 18 months. A substantial subset of these individuals have the motivation to persist on treatment over time and achieve benefit. This behavior can be reinforced in the marketplace with compliance-promoting programs.

The label comprehension data show that the level of comprehension of all key messages and warnings with the proposed label is very high (See Appendix G), and that the package circular and informational brochures further enhance comprehension. The data from the CUSTOM Study show that the vast majority of people self-select appropriately. However, a subset of people made self-selection errors of various types despite the label messages. Most of the errors centered around the multiple benefit criteria yet, by and large, the majority would benefit from the level of LDL-C lowering seen with lovastatin 20 mg. An analysis published by Dr. Eric Brass reached a similar conclusion (See Appendix F). In CUSTOM, the errors of greatest consequence, i.e., against the safety warnings, occurred with the lowest frequency. Finally, the intent of the product label for nonprescription lovastatin 20 mg is to expand safe and effective therapeutic options for primary prevention in healthy people in conjunction with standard physician-based care. Not only does the label direct people with the higher cholesterol levels and CHD risk conditions to talk to a doctor about cholesterol management, it also advises all users of

nonprescription lovastatin 20 mg to inform their doctors that they are taking the product as part of a healthy heart program. These behaviors were, in fact, seen in CUSTOM with a large percentage of consumers. A comprehensive consumer support system consistent with the one provided in CUSTOM will be implemented in the marketplace, as described in the OTC Self-Management System and Post-Launch Monitoring Plan (See Section F. MEVACOR™ OTC Self-Management System). The goal of the system is to provide consumers with tools that emphasize a "collaborative care" approach that supports self-management while ensuring proper interaction with healthcare professionals when appropriate. In this way, consumers and their physicians can partner, enabling the benefits of pharmacologic intervention for CHD reduction to be extended to a large population of Americans who choose to increase their potential for a longer, healthier life.

7. Benefit Conclusions

Benefit of Nonprescription Lovastatin 20 mg

- Access to over-the-counter lovastatin 20 mg will enable many individuals to self-manage their cholesterol and maintain health.
- Access to the MEVACOR™ OTC Self-Management System will result in greater numbers of people interacting with their physicians to discuss cholesterol and coronary heart disease. Such access will also encourage the development of heart-healthy behaviors with maintenance and improvement in both exercise habits and diet patterns.
- Availability of nonprescription lovastatin 20 mg will expand awareness of cholesterol management and cardiovascular risk factors among both the OTC-eligible and the higher CV risk population, encouraging more of the population at higher risk to seek comprehensive medical care.
- Quantitative estimates of the benefit in CHD events avoided in those self-medicating with lovastatin 20 mg over 6 years indicate that about 294 CHD events will be avoided or delayed per 10,000 people treated.
- Expansion of pharmacologic treatment for cholesterol by access to lovastatin 20 mg without a prescription will reduce the national burden of CHD.

Safety of Nonprescription Lovastatin 20 mg

- Lovastatin 20 mg has a safety profile appropriate for use in the nonprescription setting.
- Long-term, chronic use of lovastatin at prescription doses of 10 to 80 mg daily is well tolerated. In controlled clinical trials, the safety profile of lovastatin 20 to 40 mg daily is comparable to that of placebo.

- Myopathy, a dose-related toxicity of this drug class, is rare at any dose. The incidence with lovastatin 20 mg should be less than the approximated incidence of 3 cases per 10,000 people treated over a year with 40 mg in EXCEL. If concomitant interacting medications are inadvertently taken, individual risk may be increased. Myopathy is a symptomatic, reversible condition that can be managed by labeling.
- Risk of hepatotoxicity with lovastatin 20 mg is insignificant and routine measurement of transaminases is not warranted.
- With acute overdose, lovastatin has a very large margin of safety. There is no evidence of recreational abuse potential.
- While there is no evidence that inadvertent exposure to lovastatin 20 mg early in pregnancy is harmful, continued treatment during pregnancy offers no benefit to offset any potential (unrecognized) risk.

Overall Benefit to Risk of Nonprescription Lovastatin 20 mg

- The effective product labeling and reinforcement tools inherent in the MEVACOR™ OTC Self-Management System (including the package circular, educational information, and toll-free call support line to product specialists) will guide consumers toward appropriate self-selection and continued use of nonprescription lovastatin 20 mg.
- Therapeutic lifestyle patterns (such as diet and exercise) will be encouraged and maintained with the MEVACOR™ OTC Self-Management System.
- The MEVACOR™ OTC Self-Management System will encourage healthcare professional interactions for both users and non-users of the product.
- The benefit-to-risk relationship for lovastatin 20 mg is comparable to that observed with OTC low-dose aspirin therapy for the prevention of CHD.
- The overall benefits of direct access to nonprescription lovastatin 20 mg far outweigh any potential risks.

I. SUMMARY AND CONCLUSIONS

The public health of the United States is burdened by the prevalence of atherosclerotic cardiovascular disease (ASCVD), half of which is coronary heart disease (CHD). Despite therapeutic advances that have reduced the mortality rate of a CHD event, the disease remains a leading cause of mortality and disability. Preventing the first CHD event prevents the cascade of subsequent events that represent a substantial economic toll on our society. The NIH has addressed a key element of this problem by issuing the NCEP ATP III Guidelines which call for significant lifestyle changes in order to reduce LDL-cholesterol, one of the major risk factors for ASCVD. If such lifestyle changes fail, pharmacologic therapy is recommended. Despite universal endorsement of these guidelines, a profound cholesterol treatment gap exists. The result of this cholesterol treatment gap is that tens of millions of Americans for whom treatment is indicated remain untreated.

Certain statins have been demonstrated to significantly modify the development and progression of CHD for both primary and secondary prevention. The benefits of appropriate treatment with these drugs outweigh their risks.

OTC availability of a preventative medicine for an asymptomatic disorder such as elevated cholesterol is often viewed as a paradigm shift. However, consumers are already moving toward a more proactive role in managing their own health. Daily chronic therapy for an asymptomatic condition occurs now with low-dose aspirin for cardioprotection and calcium and vitamin supplements for prevention of osteoporosis. Thus, the so-called paradigm shift is more perception than reality. Additionally, the Institute of Medicine (IOM) has suggested a redesign for the shortcomings of the current U.S. health care system that also serves to address the cholesterol treatment gap. The availability of OTC MEVACOR™ through the MEVACOR™ OTC Self-Management System would be entirely consistent with the recommendations of the IOM's Quality Chasm Report. Based on the consumer healthcare movement and public health need for more consumer responsibility, the time is right for the introduction of a low dose statin into the OTC marketplace.

Lovastatin is particularly suited for primary prevention in the OTC population because of its many years of clinical experience and proven safety record. Additionally, lovastatin has been demonstrated to reduce CHD risk in an OTC-like population in the landmark AFCAPS/TexCAPS outcomes study. Over 100 million prescriptions have been written worldwide for lovastatin since 1987, providing over 27 million patient-years of treatment experience. Post-marketing monitoring of the population exposed to lovastatin over the last 17 years has provided an abundance of safety information. Both serious and non-serious adverse experiences reported are consistent with the known effects of the drug and typical underlying disease states. Serious adverse experiences are rare at the proposed 20 mg OTC dose which accounts for approximately 60% of current prescription usage, representing approximately 17.3 million patient-years of treatment. Results of the CUSTOM study demonstrate that lovastatin 20 mg is well tolerated when used by consumers in an OTC setting.

The population targeted by the MEVACOR OTC label is at risk for development of coronary heart disease and is eligible for therapy with statins based on current ATP III guidelines. Results of the CUSTOM study have demonstrated that the MEVACOR™ OTC Self-Management System enables self-selection, de-selection, and self-management of elevated cholesterol generally in accordance with the ATP III recommended LDL-C goal and guidelines. The targeted population of intermediate risk consumers is able to choose to use MEVACOR™ OTC and achieve LDL-C lowering goals, with many partnering with their physicians to achieve the maximal benefit and safety from drug therapy.

Thus, the MEVACOR™ OTC Self-Management System targets the OTC statin-eligible population and encourages a partnership with the health care professional to help reduce the cholesterol treatment gap. Effective product labeling and reinforcement tools included in the MEVACOR™ OTC Self-Management System (e.g., package circular, educational information, website, and toll-free call support line to product specialists), will guide consumers toward appropriate self-selection and continued use of nonprescription lovastatin 20 mg. Therapeutic lifestyle patterns (such as diet and exercise) are emphasized and maintained with the MEVACOR™ OTC Self-Management System.

Access to the MEVACOR™ OTC Self-Management System will result in greater numbers of people interacting with their physicians to discuss cholesterol and coronary heart disease. The availability of nonprescription lovastatin 20 mg will expand awareness of cholesterol management and cardiovascular risk factors among both the OTC-eligible and higher CHD risk population, encouraging more individuals at higher risk to seek comprehensive medical care.

The MEVACOR™ OTC Self Management System has been specifically designed to be consistent with a global approach to the cholesterol treatment gap, incorporating pharmacologic therapy with education, lifestyle changes and encouragement of a partnership with the health care professional. The availability of an OTC statin option will have a meaningful impact in improving the CHD risk status of intermediate risk Americans and thereby help to reduce the burden of CHD over the long term.

GLOSSARY OF ABBREVIATIONS

AAPCC	American Association of Poison Control Centers
ACC	American College of Cardiology
AFCAPS/TexCAPS	Air Force, Texas Coronary Atherosclerosis Prevention Study (lovastatin)
AHA	American Heart Association
ALT	Alanine aminotransferase
ARR	Absolute risk reduction
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial (atorvastatin)
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ATP III	Adult Treatment Panel III guidelines
CABS	Complementary assessment of benefit and safety
CARE	Cholesterol and Recurrent Events (pravastatin)
CHC	Chronic hepatitis C
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
CPK	Creatine phosphokinase
CUSTOM	Clinical Use Study of OTC MEVACOR™
CVA	Cardiovascular accident
CVD	Cardiovascular disease
CYP3A4	Cytochrome P-450 3A4 inhibitor
DAP	Data analysis plan
EXCEL	Expanded Clinical Evaluation of Lovastatin
HCP	Health care professional
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A (reductase inhibitor)
HPS	Heart Protection Study (simvastatin)
IOM	National Academy of Science Institute of Medicine
LCS	Label comprehension study
LD_{50}	Lethal dose-50
LDL-C	Low-density lipoprotein cholesterol

LFT	Liver function test
LIPID	Long-Term Prevention with Pravastatin in Ischaemic Disease
L-TAP	Lipid Treatment Assessment Project
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MOTC	MEVACOR OTC
MRC/BHF HPS	Medical Research Council/British Heart Foundation Heart Protection Study
NAB	Not adequate benefit
NAS	Not adequate safety
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIDDM	Noninsulin-dependent diabetes mellitus
NNT	Number needed to treat
NOS	Not otherwise specified
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter (nonprescription)
PTY	Patient treatment years
PYR	Person-years at risk
RMRS	Regenstrief Medical Record System
4S	Scandinavian Simvastatin Survival Study (simvastatin)
SOC	System organ class
TC	Total cholesterol
TERIS	Teratogen Information System
TLC	Therapeutic lifestyle change
ULN	Upper limit of normal
WAES	Worldwide Adverse Experience System (Merck's AE database)
WOSCOPS	West of Scotland Coronary Prevention Study (pravastatin)

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APPENDICES

A Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998; 279(20):1615-22.

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G MEVACOR™ Pivotal Label Comprehension Study Summary

H MEVACOR™ (Rx) US Package Circular

I MEVACOR™ OTC Labeling and Education & Support Materials

J ZOCOR HEART-PRO Support Materials

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Original Contributions

Primary Prevention of Acute Coronary Events With Lovastatin in Men and Women With Average Cholesterol Levels

Results of AFCAPS/TexCAPS

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Context.—Although cholesterol-reducing treatment has been shown to reduce fatal and nonfatal coronary disease in patients with coronary heart disease (CHD), it is unknown whether benefit from the reduction of low-density lipoprotein cholesterol (LDL-C) in patients without CHD extends to individuals with average serum cholesterol levels, women, and older persons.

Objective.—To compare lovastatin with placebo for prevention of the first acute major coronary event in men and women without clinically evident atherosclerotic cardiovascular disease with average total cholesterol (TC) and LDL-C levels and below-average high-density lipoprotein cholesterol (HDL-C) levels.

Design.—A randomized, double-blind, placebo-controlled trial.

Setting.—Outpatient clinics in Texas.

Participants.—A total of 5608 men and 997 women with average TC and LDL-C and below-average HDL-C (as characterized by lipid percentiles for an age- and sex-matched cohort without cardiovascular disease from the National Health and Nutrition Examination Survey [NHANES] III). Mean (SD) TC level was 5.71 (0.54) mmol/L (221 [21] mg/dL) (51st percentile), mean (SD) LDL-C level was 3.89 (0.43) mmol/L (150 [17] mg/dL) (60th percentile), mean (SD) HDL-C level was 0.94 (0.14) mmol/L (36 [5] mg/dL) for men and 1.03 (0.14) mmol/L (40 [5] mg/dL) for women (25th and 16th percentiles, respectively), and median (SD) triglyceride levels were 1.78 (0.86) mmol/L (158 [76] mg/dL) (63rd percentile).

Intervention.—Lovastatin (20-40 mg daily) or placebo in addition to a low–saturated fat, low-cholesterol diet.

Main Outcome Measures.—First acute major coronary event defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death.

Results.—After an average follow-up of 5.2 years, lovastatin reduced the incidence of first acute major coronary events (183 vs 116 first events; relative risk [RR], 0.63; 95% confidence interval [CI], 0.50-0.79; $P<.001$), myocardial infarction (95 vs 57 myocardial infarctions; RR, 0.60; 95% CI, 0.43-0.83; $P=.002$), unstable angina (87 vs 60 first unstable angina events; RR, 0.68; 95% CI, 0.49-0.95; $P=.02$), coronary revascularization procedures (157 vs 106 procedures; RR, 0.67; 95% CI, 0.52-0.85; $P=.001$), coronary events (215 vs 163 coronary events; RR, 0.75; 95% CI, 0.61-0.92; $P=.006$), and cardiovascular events (255 vs 194 cardiovascular events; RR, 0.75; 95% CI, 0.62-0.91; $P=.003$). Lovastatin (20-40 mg daily) reduced LDL-C by 25% to 2.96 mmol/L (115 mg/dL) and increased HDL-C by 6% to 1.02 mmol/L (39 mg/dL). There were no clinically relevant differences in safety parameters between treatment groups.

Conclusions.—Lovastatin reduces the risk for the first acute major coronary event in men and women with average TC and LDL-C levels and below-average HDL-C levels. These findings support the inclusion of HDL-C in risk-factor assessment, confirm the benefit of LDL-C reduction to a target goal, and suggest the need for reassessment of the National Cholesterol Education Program guidelines regarding pharmacological intervention.

JAMA. 1998;279:1615-1622

EPIDEMIOLOGICAL observations have demonstrated consistently a strong positive, continuous, independent, graded relation between plasma total cholesterol (TC) and the incidence of coronary heart disease (CHD). This relation covers a wide range of cholesterol concentrations, including those considered normal or mildly elevated.[1-3] In the Multiple Risk Factor Intervention Trial follow-up of screened men, 69% of deaths from CHD in the first 6 years of follow-up occurred in subjects with TC values between 4.71 and 6.83 mmol/L (182-264 mg/dL).[4] In the first 16 years of the Framingham Heart Study, 40% of participants who developed a myocardial infarction had a TC level between 5.17 and 6.47 mmol/L (200-250 mg/dL).[5]

See also pp 1643 and 1659.

Large end point studies have demonstrated conclusively that effective cholesterol-lowering treatment can substantially reduce myocardial infarction and other coronary events. In the Scandinavian Simvastatin Survival Study

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the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor simvastatin reduced total mortality in patients with CHD by 30% because of a 42% reduction in deaths from CHD.[6] Subsequently, pravastatin was shown to reduce fatal and nonfatal coronary events in patients with[7] and without[8] CHD. However, it is unknown whether benefit from reduction of low-density lipoprotein cholesterol (LDL-C) in patients without CHD (primary prevention) extends to individuals with average serum cholesterol levels, women, and older persons.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) targeted a cohort of generally healthy middle-aged and older men and women with average TC and LDL-C levels and with below-average high-density lipoprotein cholesterol (HDL-C) levels. The primary end point analysis was the incidence of first acute major coronary events, defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death. The inclusion of unstable angina was a unique feature of this study, and its inclusion as a primary end point reflects the increasing frequency of unstable angina as the initial presentation of CHD in the United States.[9]

METHODS

The design of the study has been described in detail previously.[10] In summary, AFCAPS/TexCAPS was a randomized, double-blind, placebo-controlled primary prevention trial that included 6605 men and women and was conducted at 2 sites in Texas, Lackland Air Force Base in San Antonio (n = 3737) and University of North Texas Health Science Center in Fort Worth (n = 2868).

AFCAPS/TexCAPS was powered to investigate whether long-term lipid lowering with lovastatin would decrease the rate of first acute major coronary events compared with placebo during at least 5 years of follow-up in a cohort without clinical evidence of atherosclerotic cardiovascular disease and with average TC and LDL-C levels and below-average HDL-C levels. Unstable angina was prospectively defined and required new-onset exertional angina, accelerated or rest angina, or both, and at least 1 of the following: (1) electrocardiographic findings of at least 1-mm ST-segment changes and reversible defect on stress perfusion study, (2) angiographic findings of at least 90% epicardial vessel stenosis or at least 50% stenosis in the left main coronary artery (without exercise testing), or (3) at least 1-mm ST-segment changes with pain on electrocardiographic stress testing and/or rest electrocardiograph and evidence of at least 50% stenosis in a major epicardial vessel.

Secondary objectives were to investigate whether long-term treatment with lovastatin, compared with placebo, would decrease cardiovascular morbidity and mortality across the spectrum of clinical events by measuring the rates of 7 secondary end points, including 2 components of the primary end point. The secondary end points were (1) fatal or nonfatal coronary revascularization procedures, (2) unstable angina, (3) fatal or nonfatal myocardial infarction, (4) fatal or nonfatal cardiovascular events, (5) fatal or nonfatal coronary events, (6) cardiovascular mortality, and (7) CHD mortality.

The tertiary objectives were to investigate safety, that is, whether long-term treatment with lovastatin, compared with placebo, would result in similar rates of total mortality, noncardiovascular mortality (with subset analyses for unintentional or violent death and death from cancer), fatal and nonfatal cancer (excluding basal cell and squamous cell skin cancers), and discontinuation of medication because of adverse drug effects.

Participant Recruitment and Follow-up

Men aged 45 to 73 years and postmenopausal women aged 55 to 73 years who met the lipid entrance criteria and had no prior history, signs, or symptoms of definite myocardial infarction, angina, claudication, cerebrovascular accident, or transient ischemic attack were eligible for participation in the study. Lipid entry criteria (TC, 4.65-6.82 mmol/L [180-264 mg/dL]; LDL-C, 3.36-4.91 mmol/L [130-190 mg/dL]; HDL-C, ≤1.16 mmol/L [45 mg/dL] for men or ≤1.22 mmol/L [47 mg/dL] for women; and triglycerides, ≤4.52 mmol/L [400 mg/dL]) were to be met at both 4 and 2 weeks prior to randomization, with less than 15% difference in LDL-C values. In addition, participants with LDL-C values between 3.23 and 3.34 mmol/L (125-129 mg/dL) were included when the ratio of TC to HDL-C was more than 6.0. We excluded volunteers with uncontrolled hypertension, secondary hyperlipidemia, or type 1 or type 2 diabetes mellitus that was either managed with insulin or associated with a glycohemoglobin level of at least 10% (20% above the upper limit of normal). Additionally, volunteers were excluded if, according to the 1983 Metropolitan Life Insurance tables, they had a body weight of more than 50% greater than the desirable limit for height. All participants provided written informed consent.

The Data and Safety Monitoring Board and the institutional review boards of the 2 participating centers approved the consent form and protocol. The study was conducted under the supervision of a steering committee. Administrative, clinical, and data management was performed by a contract research organization with staff at each site who were under the supervision of the clinical investigator. All personnel involved in participant care were blinded to treatment assignment and lipid levels.

Participants who met entrance criteria and completed a 12-week American Heart Association Step I diet run-in, including a 2-week placebo baseline run-in, were randomized to treatment with either lovastatin, 20 mg/d, or matching placebo. Participants in the lovastatin group were titrated to 40 mg/d if their LDL-C level was more than 2.84 mmol/L (110 mg/dL) at the 3-month study visit. The blind was maintained by titrating equal numbers of randomly selected placebo-group participants to 2 tablets daily. Throughout the trial, dietary reinforcement and other risk factor modification information was provided.

An extensive safety evaluation was performed prior to treatment, at 1 year, and at each subsequent year-end visit. Clinical visits were every 6 weeks for the first year. After 1 year, all randomized participants who continued the study drug were seen semiannually. Participants who discontinued use of the study drug were contacted on an annual basis for follow-up by questionnaire, which included an assessment of possible end point events and cancer occurrence. End point event information was compiled and adjudicated in the same manner for all participants, including those who had withdrawn from the study. An end point committee, blinded to treatment-group assignment and not involved in participant care, used prespecified criteria to adjudicate all end point events.

For analyses of changes in lipids, frozen serum samples obtained on the date of randomization before active treatment (day 1) and at the 1-year visit (post-treatment) were assayed at a specialized lipid laboratory at Johns Hopkins University, Baltimore, Md. This laboratory also analyzed lipids for the National Health and Nutrition Examination Survey (NHANES) III as noted by Sempos et al[11] (also P. S. Bachorik, PhD, unpublished data, 1997). The laboratory was standardized for lipid and lipoprotein measurements through the Centers for Disease Control and Prevention–National Heart, Lung, and Blood Institute Lipid Standardization Program.[12] All LDL-C values were calculated based on the Friedewald estimation.[13]

Statistical Analysis

The size of the sample was designed to provide 90% to 97% power to detect a 30% to 35% reduction in the number of participants with primary end point events by treatment with lovastatin. All analyses were performed on an inten-

tion-to-treat basis and all P values were 2-sided. A log-rank test, with study center and sex as stratification factors, was used to assess the effect of therapy on the rate of primary end point events. Analyses of relative reductions in risk resulting from lovastatin therapy were calculated using the Cox proportional hazards regression model that had study center and sex as stratification factors. The proportionality assumption was met for all Cox models. Cumulative incidence and interval estimates were calculated using the life-table method.

The effect of therapy on percent change in lipid parameters from baseline to 1 year was assessed using an analysis of variance model that included treatment, study center, and sex after first examining a model that also included the treatment-by-center and treatment-by-sex interaction effects. All participants with data at both baseline and 1 year were included.

The proportions of participants who discontinued therapy because of adverse events or had clinically important adverse events or laboratory abnormalities were compared between the 2 treatment groups using the Fisher exact test.

The trial was designed to continue until a total of 320 participants had experienced a first primary end point event or for a minimum of 5 years after the last participant was randomized, whichever occurred later. In addition to the final analysis, 2 interim analyses of the trial were planned for the points at which 120 and 240 participants, respectively, experienced the first primary end point event. A group sequential design was used with an early stopping rule, described previously,[10] which preserved the type I error probability of .05. The critical values for finding statistical significance for 120, 240, and 320 participants with primary end points were .003, .016, and .044, respectively.

RESULTS

Early Termination for Efficacy

Following a review of the second interim analysis (data from 267 participants who had experienced a primary end point event), the Data and Safety Monitoring Board recommended that the trial be stopped early for efficacy. The voting members of the steering committee agreed unanimously on July 3, 1997, to accept the recommendation for early termination. The steering committee required that the participants and personnel continue to be blinded throughout the final visit of the study to provide unbiased assessment of all additional end point and safety information in the final analysis. End point status was determined for all but 1 active participant within 3 months of the decision to stop the study (Figure 1).

Baseline Characteristics

Beginning May 30, 1990, and ending February 12, 1993, 6605 participants were randomized to treatment with lovastatin (2805 men and 499 women) or placebo (2803 men and 498 women). For comparison with the age- and sex-matched US population without clinical evidence of cardiovascular disease, the NHANES III percentile is presented for average baseline lipid levels.[14] Baseline lipid levels were similar in both treatment groups; combined averages were as follows: mean (SD) TC, 5.71 (0.54) mmol/L (221 [21] mg/dL) (51st percentile); mean (SD) LDL-C, 3.89 (0.43) mmol/L (150 [17] mg/dL) (60th percentile); mean (SD) HDL-C, 0.94 (0.14) mmol/L (36 [5] mg/dL) for men and 1.03 (0.14) mmol/L (40 [5] mg/dL) for women (25th and 16th percentiles, respectively); and median (SD) triglycerides, 1.78 (0.86) mmol/L (158 [76] mg/dL) (63rd percentile). The 2 treatment groups were also balanced with respect to baseline demographics, risk factors, and medications (Table 1). A more detailed description of the baseline characteristics of the study cohort in comparison with the US NHANES III reference population is provided elsewhere.[15]

Adherence and Dropouts

The mean (SD) duration of follow-up was 5.2 (0.9) years (range, 0.2-7.2 years) for those treated with lovastatin and 5.2 (0.9) years (range, 0.1-7.2 years) in the placebo group. As assessed by pill counts, 99% of participants adhered to their study regimen for at least 75% of the time that they were receiving active treatment. Study drug regimens were maintained until trial termination by 2335 (71%) of the 3304 participants randomized to lovastatin and by 2081 (63%) of the 3301 randomized to placebo (Figure 1). Participants treated with placebo were more likely to be withdrawn from the study as a result of developing CHD or starting cholesterol-reducing medication (generally at the request of their primary care physician). The frequency of discontinuation for other reasons was similar between treatment groups.

Lipid Parameters

Lovastatin had a significant effect on changes in lipid levels from baseline (day 1) to posttreatment as assessed at 1 year ($P<.001$). Low-density lipoprotein cholesterol levels were reduced by 25%, TC levels were reduced by 18%, triglyceride levels were reduced by 15%, HDL-C levels were increased by 6%, and the ratios of TC to HDL-C and LDL-C to HDL-C were decreased by 22% and 28%, respectively. By comparison, in the placebo group, there were small changes in lipid levels that were not clinically important (Figure 2). Treatment effects were similar in men and women (Table 2).

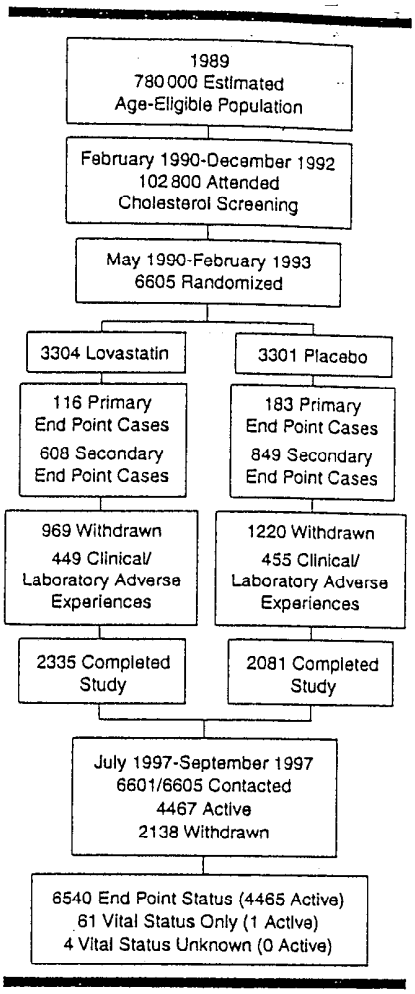

Figure 1.—Study chronology.

In the lovastatin group, 1657 participants (50%) were titrated from 20 mg/d to 40 mg/d, and of these, no participant was subsequently back-titrated. At 1 year, 1216 participants (42%) receiving lovastatin and 86 (3%) receiving placebo reached the study target for LDL-C values of no more than 2.84 mmol/L (110 mg/dL); 2334 participants (81%) receiving lovastatin and 350 (12%) receiving placebo reached an LDL-C level of 3.36 mmol/L (130 mg/dL) or less.

Efficacy End Points

Participants treated with lovastatin experienced a 37% lower incidence of the first acute major coronary event (primary end point defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) than did those treated with placebo (Cox model 95% confidence interval, 21%-50%; $P<.001$).

Table 1.—Baseline Characteristics and Medications for Study Cohort by Treatment Group*

Baseline Characteristic	Placebo (N = 3301)	Lovastatin (N = 3304)
Men aged 45-73 y, No. (%)	2803 (85)	2805 (85)
Women aged 55-73 y, No. (%)	498 (15)	499 (15)
Age, mean (SD), y	58 (±7)	58 (±7)
Men	57 (±7)	58 (±7)
Women	63 (±5)	62 (±5)
≥65 y, No. (%)	701 (21)	715 (22)
Men	515 (18)	549 (20)
Women	186 (37)	166 (33)
Race, No. (%)		
White	2935 (89)	2925 (89)
Black	101 (3)	105 (3)
Hispanic	240 (7)	247 (7)
Weight, mean (SD), kg		
Men	86.4 (±11.36)	86.8 (±11.82)
Women	70.5 (±10.9)	70.9 (±10.9)
Body mass index, mean (SD), kg/m²		
Men	27.0 (±3.0)	27.1 (±3.1)
Women	26.4 (±3.8)	26.4 (±3.5)
Blood pressure, mean (SD), mm Hg		
Systolic	138 (±17)	138 (±17)
Diastolic	78 (±10)	78 (±10)
Heart rate, mean (SD), beats/min	69 (±11)	69 (±11)
No. (%) who consume alcohol		
Men	1450 (52)	1366 (49)
Women	129 (26)	153 (31)
No. of drinks/wk, mean (SD)	5.9 (±6.3)	6.1 (±6.1)
Men	6.2 (±6.4)	6.3 (±6.2)
Women	3.0 (±3.5)	3.5 (±3.7)
NCEP CHD risk factors, No. (%)†		
Hypertension‡	729 (22)	719 (22)
Diabetes		
Non–insulin-treated diabetes	71 (2.0)	84 (3.0)
Non–insulin-treated diabetes or fasting blood glucose ≥6.99 mmol/L (126 mg/dL)	113 (3.4)	126 (3.8)
Current smoker	389 (12)	429 (13)
Family history of premature CHD	538 (16)	497 (15)
HDL-C <0.91 mmol/L (<35 mg/dL)	1146 (35)	1150 (35)
Medications, No. (%)		
Antihypertensives	695 (21.1)	661 (20.0)
ACE inhibitors	257 (7.8)	244 (7.4)
α-Blockers	67 (2.0)	68 (2.1)
β-Blockers	156 (4.7)	141 (4.3)
Calcium channel blockers	170 (5.1)	171 (5.2)
Diuretics	203 (6.1)	203 (6.1)
Estrogen with or without progestins§	137 (27.5)	155 (31.1)
Nonsteroidal anti-inflammatory drugs	445 (13.5)	494 (15.0)
Oral hypoglycemics	43 (1.3)	41 (1.2)
Thyroid replacement hormone	107 (3.2)	132 (4.0)
Aspirin	561 (17.0)	571 (17.3)

*NCEP indicates National Cholesterol Education Program; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; and ACE, angiotensin-converting enzyme.
†All Air Force/Texas Coronary Atherosclerosis Prevention Study participants met National Cholesterol Education Panel criteria for age-related risk (age ≥45 years for men and ≥55 years for women).
‡Hypertension includes those reporting history of hypertension and/or those treated with antihypertensive agents for hypertension.
§Data are for women only.

A total of 116 participants treated with lovastatin compared with 183 in the placebo group had at least 1 primary end point event. Results of primary and secondary end point analyses are summarized in Table 3. Participants are counted only once within a specific end point analysis; however, a participant may be included in more than 1 analysis in Table 3 if they experienced different types of end points, experienced an event that is comprised in more than 1 end point analysis (eg, the secondary end point, unstable angina, is also a component of the primary end point), or both.

Life-table plots (Figure 3) illustrate a difference between treatment groups beginning in the first year of treatment and continuing throughout the remainder of the study. These show the cumulative incidence and the number of participants at risk. By treatment year, the average risk reduction in the primary end point (acute major coronary events) with lovastatin was 43% in the first year and 12%, 30%, 41%, and 49% in the second, third, fourth, and fifth years, respectively. These yearly rates were not statistically different from each other.

For the primary end point, the event rate for subjects receiving lovastatin averaged 7 per 1000 patient-years and was 37% less than the 11 per 1000 patient-years observed for the placebo group. These rates correspond to cumulative incidences of 4.0% and 6.8% for the lovastatin and placebo groups, respectively, during the study period ($P<.001$).

For secondary end points, treatment with lovastatin resulted in significant, consistent benefit compared with placebo, including 33% reduction in revascularizations ($P=.001$), 32% reduction in unstable angina ($P=.02$), and 40% reduction in the incidence of fatal or nonfatal myocardial infarction ($P=.002$). For coronary and cardiovascular events (total fatal or nonfatal), treatment with lovastatin resulted in significant ($P=.006$ and $P=.003$, respectively) reductions of 25% compared with placebo. The category of cardiovascular events included all atherosclerotic cardiovascular events, as specified by the end point definitions, including stable angina, thrombotic cerebrovascular accidents, transient ischemic attacks, and peripheral arterial vascular disorders. For the secondary end points fatal cardiovascular events and fatal CHD events, there were too few events to perform survival analysis based on prespecified criteria (Table 3).

Figure 4 summarizes the effect of treatment on the rate of the first primary end point event for predefined factors: sex, age (*older* defined as above the median by sex: >57 years for men and >62 years for women), history of hypertension, active cigarette smoking, family history of CHD, baseline LDL-C, and baseline HDL-C. Treatment group, as well as each of these factors, demonstrated a significant association with risk (eg, smoking was positively associated with first acute major coronary events). Baseline triglyceride level ($P = .98$) and history of diabetes ($P = .34$, 155 participants with diabetes) were not significant predictors of outcome. Within a factor, the numerical rate of first acute major coronary events was similar among those treated with lovastatin in the CHD positive-risk subgroup and those treated with placebo who did *not* have the CHD risk factor (eg, lovastatin-treated smokers had rates similar to placebo-treated nonsmokers).

The effect of treatment with lovastatin on the rate of first acute major coronary

Table 2.—Treatment Effects on Plasma Lipid Levels at 1 Year*

Lipid	Placebo, Mean or Median (SD)		Lovastatin, Mean or Median (SD)	
	mmol/L	mg/dL	mmol/L	mg/dL
Mean TC	5.90 (±0.72)	228 (±28)	4.75 (±0.62)	184 (±24)
Men	5.84 (±0.70)	226 (±27)	4.71 (±0.60)	182 (±23)
Women	6.20 (±0.75)	240 (±29)	4.97 (±0.65)	192 (±25)
Mean LDL-C	4.04 (±0.63)	156 (±25)	2.96 (±0.52)	115 (±20)
Men	4.02 (±0.63)	156 (±24)	2.96 (±0.51)	114 (±20)
Women	4.16 (±0.66)	161 (±26)	3.00 (±0.57)	116 (±22)
Median triglycerides	1.84 (±0.93)	163 (±82)	1.61 (±0.82)	143 (±73)
Men	1.82 (±0.90)	161 (±80)	1.59 (±0.79)	141 (±70)
Women	2.05 (±1.13)	181 (±100)	1.84 (±0.91)	163 (±81)
Mean HDL-C	0.97 (±0.20)	38 (±8)	1.02 (±0.21)	39 (±8)
Men	0.96 (±0.20)	37 (±8)	1.00 (±0.20)	39 (±8)
Women	1.05 (±0.21)	41 (±8)	1.11 (±0.21)	43 (±8)

*Data are for paired samples. Sample sizes are 2387-2495 for men and 420-439 for women. TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.

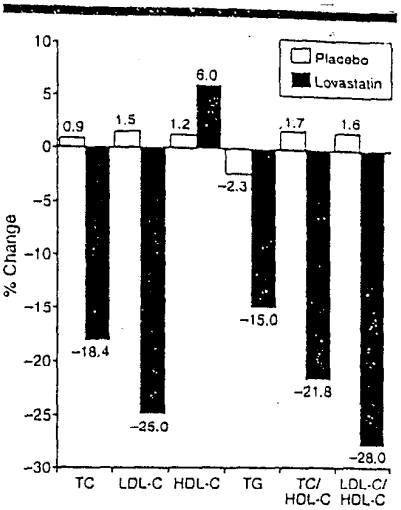

Figure 2.—Comparison of percent change in lipid parameters from baseline to 1 year by treatment group. All differences between treatment groups were significant ($P<.001$). TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and TG, triglycerides.

events was numerically greater in women than in men (46% vs 37% reduction in relative risk); however, the actual number of women who had a primary end point event was small (20 of 997), and there were no statistical differences in treatment effects between sexes. None of the subgroups differed significantly in treatment benefit (eg, treatment benefit was not different for participants with hypertension compared with participants without hypertension and benefit was not different for smokers compared with nonsmokers, since none of the treatment-by-subgroup interactions were significant). There were no significant interactions between treatment and either LDL-C ($P = .99$) or HDL-C ($P = .16$) when evaluated as continuous variables in a model with the other associated covariates. No threshold to benefit was observed in LDL-C and HDL-C ranges studied.

In addition to the protocol-specified rates that considered time to the first event for withdrawn and active participants, we also analyzed the total number of events experienced by active and withdrawn participants including multiple events of the same type (eg, multiple myocardial infarctions experienced by a participant). There were 142 and 209 acute major coronary events in participants treated with lovastatin and placebo, respectively, with rates of 8 and 12 per 1000 patient-years, respectively. There were 137 and 195 coronary revascularizations (8 and 11 per 1000 patient-years) in participants treated with lovastatin and placebo, respectively. Combining acute major coronary events and coronary revascularizations, there were 279 and 404 (16 and 23 per 1000 patient-years) in the lovastatin and placebo groups, respectively. If 1000 men and women were treated with lovastatin for 5 years, approximately 19 acute major coronary events (12 myocardial infarctions and 7 presentations of unstable angina) and 17 coronary revascularizations could be prevented.

Tolerability and Safety

Overall, treatment with lovastatin was well tolerated. Mortality and incidence of fatal and nonfatal cancer (tertiary end points to assess safety) did not demonstrate any difference between treatment groups. The overall mortality rate was similar in each group, with 80 deaths among participants treated with lovastatin and 77 deaths among participants treated with placebo (4.6 and 4.4 per 1000 patient-years in participants treated with lovastatin and placebo, respectively). The majority of deaths had noncardiovascular causes. There were 17 deaths from cardiovascular causes among participants treated with lovastatin and 25 in the placebo group (1.0 and 1.4 per 1000 patient-years in lovastatin and placebo groups, respectively) and 63 deaths from noncardiovascular causes among participants treated with lovastatin and 52 in the placebo group (3.6 and 3.0 per 1000 patient-years among participants treated with lovastatin and placebo, respectively). There were 4 deaths from trauma, 3 in the placebo group and 1 in the lovastatin group.

The overall incidence of fatal and nonfatal cancer, excluding nonmelanoma skin cancers, was 15.1 and 15.6 per 1000 patient-years (252 and 259 cases) among participants treated with lovastatin and placebo, respectively. The most frequently reported tertiary end point cancers are summarized in Table 4. The number of participants reporting nonmelanoma skin cancers, predominantly diagnoses of basal cell and squamous cell cancers, was 250 (7.6%) in the lovastatin group and 243 (7.4%) in the placebo group.

The number of participants with any adverse experience that led to discontinuation was 449 (13.6%) in the group treated with lovastatin and 445 (13.8%) in the placebo group. Both treatment groups had similar numbers of adverse experiences that were considered serious (ie, life-threatening, causing death or a permanent disability, resulting in or prolonging hospitalization, or diagnosis of any cancer), 1131 (34.2%) and 1126 (34.1%) in the groups treated with lovastatin and placebo, respectively. One participant from each treatment group was unblinded after discontinuation of the study drug and before the end of the study. A placebo-treated patient, who discontinued therapy because of idiopathic hepatitis, was unblinded because a primary care physician advised beginning lipid-reducing treatment. Another participant was unblinded when he developed study drug–related Stevens-Johnson syndrome after approximately 9 months of treatment with lovastatin. Following appropriate treatment and within 2 weeks of discontinuing lovastatin use, this participant recovered. No other lovastatin-related, life-threatening, serious, adverse experiences were reported.

Consecutive elevations of more than 3 times the upper limit of normal in either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) were rare, and the incidence was similar in both treatment groups (18 [0.6%] of 3242 participants and 11 [0.3%] of 3248 receiving lovastatin and placebo, respectively). (Not all participants had postrandomization tests.) Examining these elevations by final dose for those who were titrated also revealed no significant trends. Consecutive elevations of more than 3 times the upper limit of the normal range in

Table 3.—Efficacy End Points*

End Points	Placebo (N = 3301) n	Placebo (N = 3301) Rate§	Lovastatin (N = 3304) n	Lovastatin (N = 3304) Rate§	Relative Risk (95% CI)†	P Value‡
Primary end point: acute major coronary events defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death	183	10.9	116	6.8	0.63 (0.50-0.79)	<.001
Secondary end points						
Revascularizations	157	9.3	106	6.2	0.67 (0.52-0.85)	.001
Unstable angina	87	5.1	60	3.5	0.68 (0.49-0.95)	.02
Fatal and nonfatal myocardial infarction	95	5.6	57	3.3	0.60 (0.43-0.83)	.002
Fatal and nonfatal cardiovascular events	255	15.3	194	11.5	0.75 (0.62-0.91)	.003
Fatal and nonfatal coronary events	215	12.8	163	9.6	0.75 (0.61-0.92)	.006
Fatal cardiovascular events	25	1.4	17	1.0	...	...
Fatal CHD events	15	0.9	11	0.6	...	...

*CI indicates confidence interval; CHD, coronary heart disease; and ellipses, too few for survival analysis.
†To calculate risk reduction, subtract relative risk from 1. Relative risk and confidence interval calculated with Cox proportional hazards model.
‡P value calculated with log-rank test and adjusted for the interim analysis for the primary end point only. P values for secondary end points are unadjusted.
§Rate per 1000 patient-years.

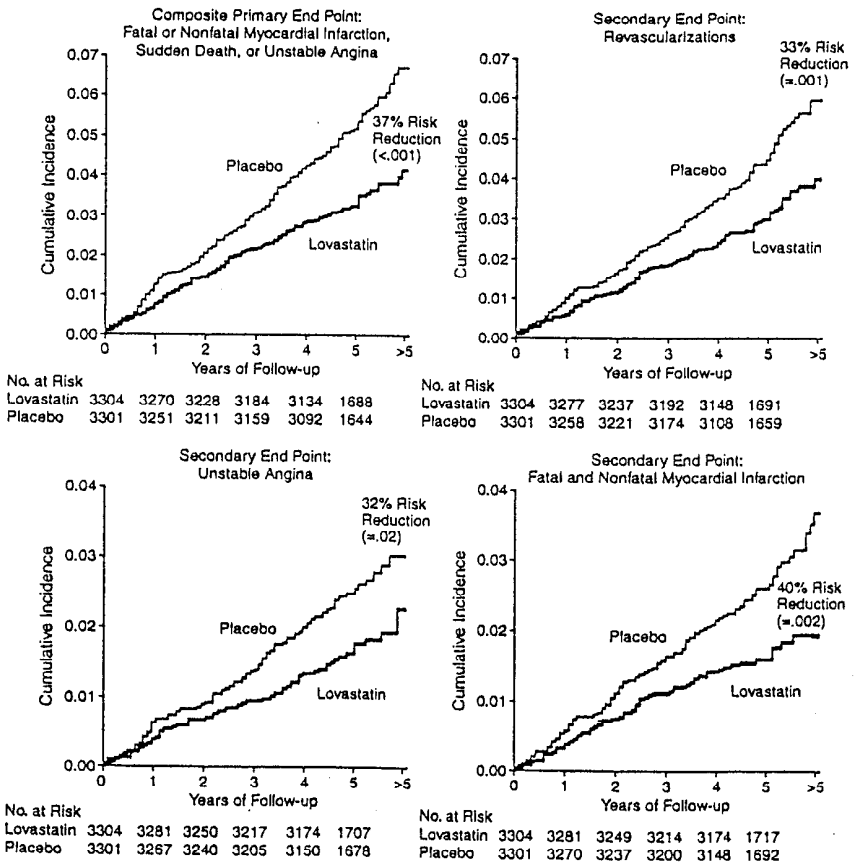

Figure 3.—Cumulative incidence of primary end points (composite of fatal and nonfatal myocardial infarction, sudden death, and unstable angina) and secondary end points (fatal and nonfatal myocardial infarction, unstable angina, and coronary revascularizations) by treatment group.

either AST or ALT were reported in 11 (0.7%) of 1585 participants and 7 (0.4%) of 1657 receiving lovastatin, 20 mg/d, and lovastatin, 40 mg/d, respectively. (Unlike the other comparisons of randomized treatment groups, the dose comparisons are of nonrandomized groups.) The number of participants with any drug-attributable AST elevation above the upper limit of normal was similar between treatment groups (33 [1.0%] and 34 [1.0%] in the groups treated with lovastatin and placebo, respectively); however, the number with any ALT drug-related elevations was significantly ($P = .003$) higher in the group treated with lovastatin (110 [3.3%] and 70 [2.1%] for lovastatin and placebo, respectively). The percentage of participants reporting myalgia leading to discontinuation was 0.3% for both treatment groups.

Creatine kinase (CK) elevations greater than 10 times the upper limit of normal were rare, and the incidence was similar in both treatment groups (11 [0.7%] of 1586, 10 [0.6%] of 1657, and 21 [0.6%] of 3248 receiving lovastatin, 20 mg/d, lovastatin, 40 mg/d, and placebo, respectively). (Denominators are participants having postrandomization tests; unlike the other comparisons of randomized treatment groups, the dose comparisons are of nonrandomized groups.) There were no cases of myopathy (defined as muscle symptoms accompanied with CK elevations >10 times the upper limit of normal). There were 3 cases of rhabdomyolysis; 2 cases occurred in placebo-treated participants, and 1 case occurred in a participant treated with lovastatin following surgery for prostate cancer.

COMMENT

In AFCAPS/TexCAPS, treatment with lovastatin resulted in a 37% reduction ($P<.001$) in the risk for first acute major coronary events, defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death. The study was originally powered to detect a 30% difference between the treatment groups after 320 participants had experienced a primary event; however, the benefit after the second interim analysis (with 267 participants experiencing an event) was of such magnitude that the predefined conditions for stopping the study were met. The differences between the 2 treatment groups appeared as early as 1 year (40 participants with events in the placebo group vs 23 treated with lovastatin).

Analysis of secondary end points confirmed that the composite primary end point was representative of its components: lovastatin therapy significantly reduced the risk for fatal or nonfatal myocardial infarction by 40% and unstable angina by 32%. Risk reduction with lovastatin across the spectrum of cardiovascular events was further confirmed by a 33% risk reduction in the need for revascularizations ($P = .001$) and 25% risk reductions in both total cardiovascular and total coronary events ($P \leq .006$). The number of deaths in AFCAPS/TexCAPS was low (157 total deaths; 42 cardiovascular deaths, of which 26 were CHD deaths), and as predicted,[10] the study was not adequately powered to detect treatment differences in the low frequency end points of cardiovascular mortality and CHD mortality.

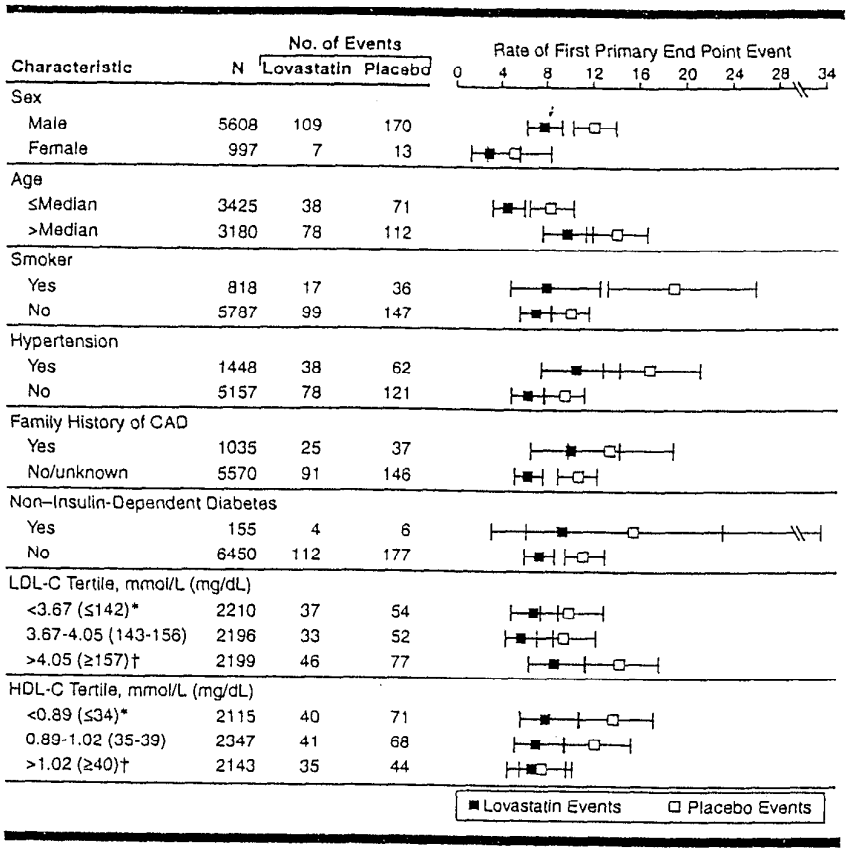

Figure 4.—Comparison of primary end point event rates (per 1000 patient-years at risk) and 95% confidence intervals by treatment within demographic and risk factor subgroups at baseline. CAD indicates coronary artery disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; asterisks, bottom tertile; and daggers, top tertile.

Primary end point risk reduction with lovastatin was apparent across all baseline LDL-C tertiles with no threshold to benefit observed across baseline LDL-C levels (range, 2.33-6.08 mmol/L [90-235 mg/dL]). Benefit was also apparent within subgroups, including women, men older than the median age (>57 years), women older than the median age (>62 years), and for participants with additional CHD risk factors. As observed in secondary prevention trials,[6,7] female AFCAPS/TexCAPS participants responded to treatment as well as, if not better than, male participants. Lovastatin appeared to attenuate (Figure 4) the risk conferred by sex, age, family history, hypertension, smoking, LDL-C levels, and below-average HDL-C levels.

AFCAPS/TexCAPS is, to our knowledge, the first primary prevention trial to demonstrate risk reduction from lipid modification in generally healthy men and women without clinical evidence of cardiovascular disease and with average TC and LDL-C levels and below-average HDL-C levels. The baseline means for TC and LDL-C (5.71 mmol/L [221 mg/dL] and 3.89 mmol/L [150 mg/dL], respectively) are similar to the average levels for age- and sex-matched individuals without cardiovascular disease in NHANES III.[14] Mean baseline HDL-C values (0.94 mmol/L [36 mg/dL] for men and 1.03 mmol/L [40 mg/dL] for women) were below the average for the NHANES III reference population; however, the HDL-C range for the cohort is 0.47 to 1.58 mmol/L (18-61 mg/dL). Only 17% of AFCAPS/TexCAPS participants would have met current National Cholesterol Education Program (NCEP) guidelines for drug therapy (TC, ≥6.21 mmol/L [240 mg/dL]; LDL-C, ≥4.14 mmol/L [160 mg/dL]; and 2 or more risk factors) and 32% would not have a fasting lipid profile measurement by current NCEP guidelines (TC, <6.21 mmol/L [240 mg/dL] without 2 or more risk factors).[16]

Earlier primary CHD prevention studies included only middle-aged men with very high TC and LDL-C concentrations.[8,17,18] In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT),[17] the upper age limit was 59 years (mean age, 47.8 years), and the mean TC, LDL-C, and HDL-C concentrations at baseline (prior to diet therapy) were 7.55 mmol/L (292 mg/dL), 5.59 mmol/L (216 mg/dL), and 1.16 mmol/L (45 mg/dL), respectively. In the Helsinki Heart Study,[18] the upper age limit was 55 years (mean age, 47.3 years), and the mean baseline lipid values for TC, LDL-C, and HDL-C were 6.98 mmol/L (270 mg/dL), 4.86 mmol/L (188 mg/dL), and 1.22 mmol/L (47 mg/dL), respectively. Likewise, the West of Scotland Coronary Prevention Study (WOSCOPS)[8] was limited to middle-aged men; the upper age limit was 64 years (mean age, 55.2 years) and the mean baseline lipid values for TC, LDL-C, and HDL-C were 7.03 mmol/L (272 mg/dL), 4.97 mmol/L (192 mg/dL), and 1.14 mmol/L (44 mg/dL), respectively. All of these trials reported statistically significant reductions in the primary end point of the combined incidence of nonfatal myocardial infarction and CHD death; the risk reductions were 19% in LRC-CPPT,[17] 34% in the Helsinki Heart Study,[18] and 31% in WOSCOPS.[8] Extrapolation of the results of these 3 trials of middle-aged men with moderate-to-severe hypercholesterolemia to the general population with lower TC and LDL-C levels, to women, and to older individuals has remained a matter of debate.[19]

Results from AFCAPS/TexCAPS are consistent with findings from previous primary prevention trials with high-risk cohorts[8,17,18]; however, treatment with lovastatin in AFCAPS/TexCAPS extends the benefit to a lower-risk segment of the general population. In contrast with earlier studies, the AFCAPS/TexCAPS cohort included Hispanics, African Americans, and older persons (baseline mean age, 58.2 years; upper limit, 73 years; 21% older than 65 years).[15] The AFCAPS/TexCAPS trial is also the first large-scale primary prevention trial of LDL-C reduction to include a substantial number of women (997 of the 6605 participants randomized). The cohort was also generally healthy, with only 12% active smokers, 22% with hypertension, and 2% with diabetes.

Inclusion of unstable angina in the primary end point analysis resulted from the observations that hospital admissions for diagnostic and surgical intervention fol-

Table 4.—Treatment Group Comparison of Participants With Cancer

Cancer	Placebo (N = 3301)	Lovastatin (N = 3304)	P Value*
All fatal and nonfatal most frequently reported	259	252	.75
Prostate	108	109	>.99
Melanoma	27	14	.04
Colon	20	25	.55
Lung	17	22	.52
Lymphoma	11	12	>.99
Bladder	11	12	>.99
Breast	9	13	.52

*P values are for between-treatment-group differences.

lowing unstable angina were increasing while myocardial infarction, as the cause for initial presentation, was decreasing.[9] AFCAPS/TexCAPS data indicate that approximately equal numbers of patients initially present with unstable angina and nonfatal myocardial infarction.

The issue of safety and drug tolerance is particularly important in primary prevention, where the risks of long-term drug therapy must be considered in the context of achievable benefit. AFCAPS/TexCAPS provides long-term safety data on a cohort treated up to 7 years with lovastatin. The withdrawal rate was comparable to that seen in other primary prevention trials,[3,18] and frequency of withdrawal for adverse experiences was similar in the treatment groups.

The results confirm and, by longer treatment duration, extend those from the Expanded Clinical Evaluation of Lovastatin (EXCEL) trial,[20] in which 8245 participants were studied for 1 year using regimens representative of the entire lovastatin dosage range. Both EXCEL and AFCAPS/TexCAPS demonstrated no cases of lovastatin-induced myopathy, no significant differences between treatment with lovastatin, 20 mg/d, and placebo in the number of participants experiencing clinically important elevations in transaminase concentrations (>3 times the upper limit of normal) and CK elevations (10 times the upper limit of normal). Furthermore, AFCAPS/TexCAPS provides reassuring data about long-term treatment with lovastatin, cancer rates, and traumatic deaths, and confirms the safety shown in other large long-term studies with simvastatin and pravastatin.[6-8]

The AFCAPS/TexCAPS results indicate that cholesterol reduction with lovastatin for men and women with average TC and LDL-C levels could potentially improve quality of life by extending CHD event-free survival and conserving invasive treatments. The economic impact of treatment requires resource utilization analyses that consider the cost of long-term treatment, hospitalization, and the cost of diagnostic and therapeutic intervention.

These findings support and extend the recommendations of the NCEP to include HDL-C in addition to TC in initial risk-factor assessment, target LDL-C reduction as the primary goal of therapy, and, if necessary, titrate treatment to achieve an LDL-C goal level. The benefit seen in all subgroups and across all tertiles of LDL-C in AFCAPS/TexCAPS occurred with 25% LDL-C reduction and suggests that treatment with lovastatin could be considered in asymptomatic participants at relatively low risk for CHD and with average TC and LDL-C levels (>3.36 mmol/L [130 mg/dL]) and below-average HDL-C levels (<1.29 mmol/L [50 mg/dL]).

AFCAPS/TexCAPS demonstrates that lovastatin, 20 to 40 mg/d, can reduce the risk for first acute major coronary events in men and women with average or mildly elevated TC and LDL-C levels and below-average HDL-C levels. Using NHANES III survey data,[14] approximately 8 million Americans without documented cardiovascular disease meet the age and lipid criteria of AFCAPS/TexCAPS. Assuming that only 17% of the reference population would qualify for drug treatment by current NCEP guidelines, we estimate that 6 million Americans currently not recommended for drug treatment may benefit from LDL-C reduction with lovastatin. These results support the inclusion of HDL-C measurement in initial risk-factor assessment and suggest reassessment of NCEP guidelines regarding pharmacological intervention.

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The Case for Over-the-Counter Statins

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In May 2004, the British government announced that it was moving forward in developing a program to provide over-the-counter (OTC) access to a small dose of the 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor simvastatin.[1] This major initiative would be 1 of the first to move a prescription drug intended for disease prevention than for symptom control to OTC status and has met with arguments in favor and against such a conversion.[2,3] The British maneuver has created a significant level of discussion about whether OTC statins would be appropriate in the American population. If so, a number of questions must be answered first: Who should qualify for such therapy? Would it be of benefit? Is it safe? Addressing these questions may illuminate the place of small-dose OTC statins in the United States.

European and United States guidelines endorse aggressive modification of risk factors in patients at highest risk for coronary heart disease (CHD), i.e., those with previous CHD, other cardiovascular disease, or diabetes.[4,5] Therefore, no argument can be made for self-medication or management without a physician's supervision in this group. However, the guidelines of Adult Treatment Panel III of the National Cholesterol Education Program identified a group of patients who require primary prevention and qualify for intervention because of their intermediate risk for near-term CHD, defined as those with multiple ($\geq$2) risk factors and a 10-year CHD risk $\leq$20%, with a goal of achieving a level of low-density lipoprotein (LDL) cholesterol of $<$130 mg/dl (3.36 mmol/L). In these patients, clinical decision making is more nebulous. Although therapeutic lifestyle changes, including diet, weight management, and physical activity, are critical recommendations for patients at intermediate risk, undertreatment of coronary risk through therapeutic lifestyle changes alone is frequently encountered.[5,6] As a complement to therapeutic lifestyle changes in this intermediate-risk group, small-dose OTC statins may be a viable approach to decrease risk based on clinical trial data. Patients ideally suited for such an OTC approach to statin therapy should be eligible according to the criteria of Adult Treatment Panel III (i.e., have multiple risk factors and a 10-year CHD risk $\leq$20%), be free of contraindications to such therapy, and have a favorable benefit-to-risk relation.

EVIDENCE FOR STATINS IN PRIMARY PREVENTION

Three large-scale, randomized, placebo-controlled, clinical studies have reported a beneficial effect of statin therapy in primary CHD prevention: the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the West of Scotland Coronary Prevention Study (WOSCOPS), and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS; Table 1).[7–9] Of these, 2 used what would have been considered a "small" dosage of the studied statin. ASCOT investigated 10 mg/day of atorvastatin, AFCAPS/TexCAPS studied 20 to 40 mg/day of lovastatin, and WOSCOPS examined the then largest available dosage of pravastatin at 40 mg/day. In addition, the 10-year CHD risks of the 3 trial populations differed. The equivalent 10-year coronary event rates (nonfatal myocardial infarction and fatal CHD or nonfatal and fatal myocardial infarction in the case of AFCAPS/TexCAPS) of the placebo-treated populations from AFCAPS/TexCAPS, ASCOT, and WOSCOPS were 5.6%, 9.4%, and 15.8%, respectively. The 5.6% 10-year CHD event rate in the placebo-treated group from AFCAPS/TexCAPS was significantly lower than any treatment threshold currently recommended for lipid-lowering drugs in the context of primary prevention.[7]

ASCOT: The lipid-lowering arm of the ASCOT assessed the clinical effect of 10 mg/day of atorvastatin versus placebo in 10,305 patients who had hypertension, a total cholesterol level $\leq$250 mg/dl (6.5 mmol/L), and a high-risk profile without previous myocardial infarction, current angina, or cerebrovascular disease within 3 months before randomization.[7] Originally planned to have a follow-up of 5 years, ASCOT ended early after a median follow-up of 3.3 years because of an interim analysis that detected a decrease in relative risk of 36% ($p = 0.0005$) in nonfatal myocardial infarction or death due to CHD for the group treated with atorvastatin versus placebo. The relative risk for stroke was decreased by 27% ($p = 0.024$) and that for total cardiovascular events was decreased by 21% ($p = 0.0005$). There was no effect on total mortality rate, and adverse event rates did not differ between treatment groups.

WOSCOPS: Using a double-blind, placebo-controlled design, WOSCOPS evaluated the effects of a fixed dose of pravastatin, 40 mg/day, or placebo over a 5-year period in men whose average age was 55 years, who had no history of documented myocardial infarction, and whose total cholesterol level was $\geq$252

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TABLE 1 Effect of Statin Therapy on Primary Prevention of Coronary Heart Disease: Clinical Events Trials

Trial (duration)	n	Statin/Dosage (mg/d)	Baseline LDL-C (mg/dl)	Decrease in LDL-C	LDL-C Achieved (mg/dl)	Statin Event* Rate	Placebo Event* Rate	RRR	ARR	NNT*
WOSCOPS[8] (4.9 yrs)	6,595	Pravastatin/40	192	26%	159	5.5	7.9	31%	2.4%	44
AFCAPS/TexCAPS[9] (5.2 yrs)	6,605	Lovastatin/20–40	150	25%	115	3.3	5.6	40%	2.3%	43
ASCOT[7] (3.3 yrs)	10,305	Atorvastatin/10	133	29%	90	6.0	9.4	36%	3.4%	33

*Primary outcomes: Nonfatal MI or CHD death in WOSCOPS; event rate is expressed as absolute percentage of risk at 5 years, as published. Nonfatal or fatal MI as a first event in AFCAPS; event rate is expressed as number of events per 1,000 patient-years, as published. Nonfatal MI and fatal CHD in ASCOT; event rate is expressed as number per 1,000 patient-years, as published.

ARR = absolute risk reduction; MI = myocardial infarction; NNT = number needed to treat; RRR = relative risk reduction.

mg/dl (6.50 mmol/L). The primary end point of WOSCOPS was the combined incidence of nonfatal myocardial infarction and death due to CHD, which was significantly decreased by 31% with pravastatin compared with placebo. No increase in noncardiovascular death rates could be demonstrated in the pravastatin group. Treatment did not appear to increase the risk for adverse events.

AFCAPS/TexCAPS: Of the clinical trials, the AFCAPS/TexCAPS studied the cohort at lowest risk for CHD, which was comprised of 6,605 middle-age men and women who had no clinical evidence of atherosclerosis, average levels of LDL cholesterol, and below-average levels of high-density lipoprotein cholesterol compared with the cohort of the Third National Health and Nutrition Examination Survey.[9] The participants ranged in age from 45 to 73 years in men and from 55 to 73 years in women. The entrance lipid criteria were cholesterol levels of 180 to 264 mg/dl (4.65 to 6.82 mmol/L), LDL cholesterol levels of 130 to 190 mg/dl (3.36 to 4.91 mmol/L), and high-density lipoprotein cholesterol levels of ≤45 mg/dl (1.16 mmol/L) in men and ≤47 mg/dl (1.22 mmol/L) in women.

Unlike the other 2 trials described in this editorial, AFCAPS/TexCAPS permitted drug titration. Lovastatin was begun at 20 mg/day and then titrated at week 18 to 40 mg/day if a LDL cholesterol target goal of 110 mg/dl (2.84 mmol/L) was not attained. In the lovastatin group, 50% of patients were titrated for this reason, and the mean on-treatment LDL cholesterol level was 115 mg/dl (2.96 mmol/L). Of the group randomized to receive lovastatin, 81% reached the Adult Treatment Panel III target goal of 130 mg/dl (3.36 mmol/L) compared with 12% of patients taking placebo. The primary end point was the rate of first acute major coronary events, defined as a composite end point including fatal or nonfatal myocardial infarction, unstable angina, and sudden cardiac death. After a median of 5.2 years, therapy with lovastatin resulted in a statistically significant 37% decrease in the incidence of a primary end point event ($p < 0.001$). Lovastatin therapy also decreased secondary end points: a 33% decrease in the risk of revascularizations ($p = 0.001$), a 32% decrease in the risk of unstable angina ($p = 0.02$), a 40% decrease in the risk of nonfatal or fatal myocardial infarctions ($p = 0.002$), and 25% decreases in the risk of coronary and cardiovascular end points ($p = 0.006$ and 0.003, respectively). The safety analysis demonstrated no increase in noncardiac mortality with lovastatin therapy, and the discontinuation rate was similar in the groups treated with placebo and lovastatin.

AFCAPS/TexCAPS is the first major clinical trial of a statin to demonstrate decreases in first coronary events in a lower intermediate-risk subgroup whose profile approximates that of the general population in the United States. These results indicate that primary prevention is clinically feasible in a lower intermediate-risk population, and the benefit was consistent across the range of baseline quartiles for LDL cholesterol.

SAFETY OF STATINS

Despite the withdrawal of cerivastatin in 2001 due to excess fatal rhabdomyolysis, the clinical trial and safety data reported to date for the statins that preceded it indicate a favorable risk-to-benefit ratio.[10] Rosuvastatin, released after cerivastatin, has clinical event trials underway. A 2002 clinical advisory issued by the American College of Cardiology, the American Heart Association, and the National Heart, Lung, and Blood Institute concludes that, when statins are appropriately used in properly selected patients, they decrease the risk of cardiovascular events, although there is the small possibility of side effects in certain patients.[11] At doses used in clinical trials, the statins have a good safety record, and 1 may assume that smaller doses would be even safer with respect to the risk of adverse experiences. Hepatotoxicity and myotoxicity are the key adverse effects that are cited with statins.

Statins appear to decrease cholesterol synthesis to a greater degree in the liver than in any other tissue.[12] Increases >3 times the upper limit of normal of the liver enzymes alanine aminotransferase and aspartate aminotransferase have been observed in about 3% of statin recipients, usually depending on the dose. The biochemical changes often resolve despite continuation of the statin. Increases in alanine aminotransferase and aspartate aminotransferase have been observed with the other classes of lipid-modifying agents, and these increases may be due to the changes in lipid metabolism induced by these drugs and not by the drugs per se. A meta-analysis of the 3 major trials of pravastatin reported identical rates of increased

alanine aminotransferase (1.4%) in groups receiving statin and placebo in the context of >112,000 person-years of exposure to that drug.[13] In AFCAPS/TexCAPS, increased rates of liver enzymes to >3 times the upper limit of normal did not differ significantly between groups receiving lovastatin and placebo. In most patients treated with lovastatin who showed consecutive increases, rechallenge with the statin was negative or the increase resolved during treatment.[14] A recent retrospective study evaluated the effects of statins on liver biochemistries over a 6-month period in patients who had high baseline levels of liver enzymes.[15] No increased risk of hepatotoxicity from statins was found among such patients compared with untreated patients.

Although baseline measurement of liver enzymes is a practical measurement for future comparisons, no data to date have made a persuasive case that routine liver enzyme measurements while on statins can predict liver injury or acute hepatocellular reactions.[16] Nevertheless, statins have been associated with rare cases of hepatocellular toxicity and jaundice. Therefore, patients who have major liver disease, heavy alcohol consumption, or chronic hepatitis should be given statins only under conditions of careful monitoring.[17]

Because of clinical experience with cerivastatin, muscle toxicity, with a worst-case scenario of rhabdomyolysis, is a more pressing concern with statins. In ASCOT, the number of serious adverse events did not significantly differ between patients assigned 10 mg/day of atorvastatin and those given placebo.[7] One patient treated with atorvastatin who had a history of high alcohol intake and a recent febrile illness developed nonfatal rhabdomyolysis. In AFCAPS/TexCAPS, small, consistent increases (median <5 IU/L) in creatine kinase were detected with lovastatin 20 to 40 mg/day compared with placebo, but the frequency of creatine kinase increases to >10 times the upper limit of normal was identical in the study groups.[14] Rhabdomyolysis occurred in 2 patients taking placebo and 1 patient receiving lovastatin; the patient receiving lovastatin had prostate cancer, and rhabdomyolysis occurred postoperatively while the patient was not receiving study medication. None of the patients reported uncomplicated myopathy (creatine kinase increases to >10 times the upper limit of normal and muscle pain). Lovastatin is metabolized by the cytochrome P450 3A4 isoenzyme pathway, and co-therapy with drugs that compete for metabolism by this pathway is a hypothetical explanation for adverse interactions between drugs. However, there were no treatment group differences in AFCAPS/TexCAPS in the frequency of clinically important muscle-related adverse events in patients who received lovastatin and used cytochrome P450 3A4 inhibitors (n = 535) compared with those taking placebo (n = 511).

Although these data paint a favorable portrait of statin treatment, patients who are included in clinical trials may be more likely to be treated in accordance with recommended practice and may be different from those seen in general practice. For example, clinical trial protocols often exclude patients who may be more prone to myopathy (e.g., the elderly) or who may have abnormal baseline results on liver tests. It is reasonable to suspect that, in the final picture, the incidence of side effects may be higher in clinical situations in which patients are not monitored as closely as they are in clinical trials.[11]

Nevertheless, the potential for myopathy or hepatoxicity with the currently approved statins is outweighed in most patients by the potential protection against coronary and cardiovascular events associated with statins. The risk of myopathy may be expected to increase in frail elderly patients, especially women; in patients who have diabetes complicated by chronic renal failure; in patients in the perioperative phase after surgery; in those with liver disease; and in association with specific concomitant medications.[11] For these patients who would require some clinical supervision, small-dose OTC statin self-medication would likely be an inappropriate approach.

Conclusion: Statin therapy is at the forefront of drug approaches to the management of lipid disorders and the prevention of coronary events. The potential conversion of a small-dose statin to OTC status raises a number of intriguing questions and opportunities. In November 2003, *The Wall Street Journal* highlighted several of these challenges in a front-page article.[18] Would OTC status get statins to more of the patients who need them? Would the safety risks be minimal? Would consumers be able to take the drugs properly and handle the risks of side effects? Would patients who need more aggressive treatment or clinical monitoring be prevented from self-medicating? A large clinical use study of such an OTC statin is to be released later this year and may address these questions with regard to consumer behavior (Jeffrey Melin, MD, personal communication April 7, 2004).

There has been success in the primary prevention of high levels of blood cholesterol in the United States,[19] but there are many areas for improvement. In the United States, CHD remains the leading killer of men and women, and the economic burden of coronary and other cardiovascular diseases is staggering: $368.4 billion in estimated direct and indirect costs.[20] Even in patients who have the highest risk and are under a physician's care, treatment is often underused and out of line with guidelines.[21–27] Therapeutic lifestyle changes, the absolute cornerstone of prevention recommendations, are nevertheless challenged by difficulties with compliance and only a modest effect on risk factor values. There is clearly a desire for complementary approaches to lifestyle therapy based on the amount of money spent on vitamin supplements and other OTC products with poor bona fides as preventive medicine.[28–30] An OTC version of a statin with demonstrated primary-prevention benefits will offer another therapeutic alternative for patients who have intermediate risk and require primary prevention. The decision in the United Kingdom to permit OTC statins makes the debate a timely and important one for the United States.

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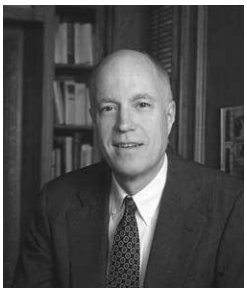
FROM THE EDITOR

Over-the-Counter Statin Drug



The statin drugs are the most effective drugs ever created for preventing and arresting atherosclerosis, the biggest killer of adults in the Western World. Indeed, it can be said that the statin drugs are to atherosclerosis what penicillin was to infectious disease. The first statin, namely, lovastatin (Mevacor), was introduced in the USA in 1987, and subsequently, 6 others (pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin [withdrawn 4 years later], and rosuvastatin) have appeared. Several 2-, 3-, and 5-year studies have shown that these drugs are enormously effective in preventing first and repeat atherosclerotic events. Despite the proven effectiveness of these drugs, they are underutilized in patients with proven atherosclerotic events, in patients with diabetes mellitus, and in subjects with particular risks of developing these events. A group particularly neglected for this therapy are subjects whose serum low-density lipoprotein (LDL) cholesterol is from 130 to 170 mg/dl and who are free of an atherosclerotic event and of diabetes mellitus. An estimated 18 million Americans are at this risk level and are eligible for lipid-lowering therapy. Unfortunately, only about 4 million of them are currently on lipid-lowering therapy.

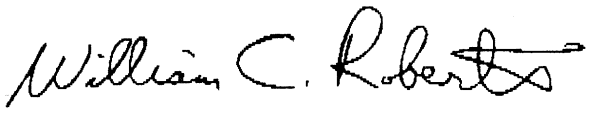
Three randomized controlled mega trials now unequivocally demonstrate reduction in risk of atherosclerotic events in primary prevention: the West of Scotland Coronary Atherosclerosis Prevention Study (WOSCOPS), the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/Tex CAPS), and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT); these trials also show that these drugs are quite safe (rhabdomyolysis in 1/10,000 users).

In an attempt to fill this treatment gap in patients at low to moderate risk, 2 pharmaceutical companies (Johnson & Johnson/Merck and Bristol Myers Squibb [BMS]) have approached the Federal Drug Administration (FDA) regarding the possibility of making available a statin drug for over-the-counter (OTC) use. In 1998, the Mevacor OTC Board of Advisors of Johnson & Johnson/Merck was formed.* This advisory board has met biannually since 1998. The first switch application was submitted to the FDA in 1999 for lovastatin 10 mg and (by BMS) for pravastatin 10 mg. The FDA's Advisory Committee in July 2000 recommended further study of consumer behavior and more proof of benefit in the target population.

As a consequence of the compelling AFCAPS/Tex CAPS data, which included 6,605 intermediate risk patients (10-year risk for coronary heart disease of $\leq$20% and $\geq$2 atherosclerotic risk factors) treated with 20 to 40 mg/day of lovastatin and resulted in a 37% relative risk reduction for a first major coronary event, the Mevacor OTC group, with input from the FDA, recommended increasing the OTC lovastatin dose to 20 mg daily for low to moderate risk populations based on the National Cholesterol Education Committee's Adult Treatment Panel III guidelines. Additionally, Mevacor Self-Management System was developed to educate and guide appropriate consumer behavior.

The result was the CUSTOM trial, which is described in detail in this issue. The CUSTOM trial in essence demonstrates that most consumers appropriately chose whether or not to use Mevacor OTC, that most users achieved beneficial lipid lowering with lovastatin 20 mg (comparable to that seen in randomized controlled clinical trials), that most consumers appropriately managed their treatment over time, that the Mevacor OTC Self-Management System generated large numbers of consumer interactions with health care professionals (as directed by the label), that heart-healthy lifestyle behaviors (diet and exercise) were maintained or improved, and that consumers can safely manage their use of Mevacor OTC over time.

While the CUSTOM study was being reviewed for publication, simvastatin (Zocor) 10 mg became available to the public in the United Kingdom without a prescription. The UK government hopes making it easier for individuals to acquire a low-cost statin ($<$\$1.00 per day) will increase the drug's use and reduce cardiovascular mortality and morbidity in that nation. The UK is the first nation to approve over-the-counter statin availability. If lovastatin is approved for OTC use in the USA, it will be the first drug approved in this manner for *long-term* use, not for an acute condition. I hope the FDA in 2005 will look favorably for OTC statin therapy also in the USA.



*WCR serves on the Mevacor OTC Board of Advisors of Johnson & Johnson/Merck and has done so since 1998. He also has served in an advisory capacity to Pfizer for selected studies. He has received grants in the past from Parke-Davis (Pfizer) and Bristol-Myers-Squibb. He is on the teaching faculties of several pharmaceutical companies, including Merck, Merck/Schering Plough, Schering Plough, Pfizer, and AstraZeneca. He does not own stock in any pharmaceutical or medical device company.

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A Consumer Use Study of Over-the-Counter Lovastatin (CUSTOM)

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The Consumer Use Study of OTC Mevacor evaluated the ability of subjects to self-manage high levels of low-density lipoprotein (LDL) cholesterol by using a multifaceted cholesterol self-management program (the Mevacor* Over-the-Counter Self-Management System; MOTC-SMS). This 26-week all-comers multicenter observational study was conducted in naturalistic storefront settings that used the fully functional MOTC-SMS to guide subjects' behavior. Of 3,316 subjects who evaluated the product (evaluators), 1,061 took ≥1 20-mg tablet of Mevacor OTC (users). Eighty-four percent of evaluators made appropriate initial use decisions. Most users demonstrated acceptable ongoing use behavior regarding treatment to goal, compliance/persistence, changes in health status, dietary patterns, and exercise habits. Throughout the study, 23 users (2%) demonstrated behavior that created the potential for suboptimal safety. After 26 weeks, median levels of LDL cholesterol were reduced by 25% among users who fasted. Of the 878 users who completed the study lipid test, 548 (62%) achieved the LDL cholesterol target goal (<130 mg/dl). Physician interactions were common. Mevacor OTC was well tolerated, with no observable adverse experiences from drug interactions or reports of myopathy. This actual use study demonstrates that the MOTC-SMS can effectively guide consumers to interact with health care professionals and to make appropriate initial and ongoing use decisions to manage their elevated levels of LDL cholesterol, with minimal potential or actual safety risk. ©2004 by Excerpta Medica, Inc.

(Am J Cardiol 2004;94:1243–1248)

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) has emphasized the importance of primary prevention of coronary heart disease (CHD), especially among individuals with multiple risk factors (≥2) for CHD.[1] Individuals with ≥2 risk factors for CHD and whose calculated 10-year risk of CHD is ≤20% are considered to be at intermediate risk. Extrapolating from recent data derived from the National Health and Nutrition Examination Survey III, the intermediate-risk population comprises >23 million Americans.[2] Despite ATP III guidelines, most of this population remains untreated with lipid-lowering agents with a cholesterol treatment gap of ≥62%.[3,4] One possible approach to narrowing the cholesterol treatment gap among the intermediate-risk population is through the availability of an over-the-counter (OTC) statin. Lovastatin, the first marketed statin, was approved in the United States in 1987 and is currently being developed for OTC availability as Mevacor OTC 20-mg tablets (MOTC). To determine whether patients could self-manage cholesterol using a multifaceted cholesterol self-management program, a 26-week observational study, the Consumer Use Study of OTC Mevacor (CUSTOM), was undertaken.

METHODS

Study design: CUSTOM was an open-label, uncontrolled, "all-comers," multicenter, use study conducted to observe consumers' initial use (self-selection) and ongoing use (de-selection) behavior in a naturalistic retail setting. Participants were recruited by mass media advertising to 14 storefront sites in 7 geographic areas of the United States. Advertising was developed to attract a population concerned about their cholesterol levels. Interested participants were requested to purchase the product as they would in a true retail setting. MOTC is intended to be sold in retail locations that have pharmacy personnel on site during normal business hours to answer consumer questions about the product. Therefore, the nurse investigators for the clinical study assumed the role of trained pharmacists.

A fully functional Mevacor OTC Self-Management System (MOTC-SMS) was available to guide consumer behavior regarding cholesterol self-management. The MOTC-SMS included shelf displays, the product carton, package insert, Quick Start Guide with physician and pharmacist notification cards, brochure, product Web site, toll-free call center, cholesterol testing referral service, and a Consumer Assistance Program. The MOTC-SMS focused on the primary prevention of CHD in a subset of individuals with multiple risk factors that approximated those of the intermediate-risk population and encouraged dialog between the consumer and the physician about cho-

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*Mevacor is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey.

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lesterol and therapy with MOTC. The MOTC carton label was designed to be consistent with the ATP III guidelines. The nurse investigator was explicitly instructed not to volunteer any information that could assist the participant in the self-selection process. Only when requested did the nurse investigator answer questions and/or perform an eligibility assessment (a scripted interview to assess medical history according to label criteria to assist participants in determining whether MOTC was right for them). If an eligibility assessment was not requested, 1 was performed at the final study visit, after all behavior questions had been answered, to determine the participant's eligibility for MOTC and evaluate self-selection behavior.

The MOTC label requires that consumers know their levels of high-density lipoprotein cholesterol, low-density lipoprotein (LDL), and triglycerides. If participants inquired about the on-site cholesterol testing service, they could purchase a cholesterol test (performed by fingerstick and a desktop analyzer). Signs in the study site indicated that testing after fasting would produce the most accurate results. Participants could choose to leave the site to fast before obtaining a cholesterol test (on site or elsewhere), obtain previous cholesterol values, and/or talk to a physician.

All individuals who evaluated the MOTC-SMS at the study site were termed "evaluators." Those who chose to purchase MOTC were termed "purchasers," and those who took ≥1 dose of MOTC were termed "users." Evaluators who did not purchase the drug were termed "nonpurchasers," and purchasers who did not use the drug were termed "purchasers, nonusers." "Self-selection" describes the initial use decision of the evaluator. "De-selection" refers to the ongoing use decisions of the user over the 26 weeks of the study with regard to obtaining a follow-up cholesterol test and resultant behavior, new prescription medications, new medical conditions, and occurrence of unexplained muscle pain.

Purchasers were able to purchase 1 to 4 cartons (45-day supply/carton) of the study drug (20 mg of lovastatin). The study drug was packaged in cartons printed with the proposed market label, which included detailed directions for use (Table 1). All purchasers underwent informed consent after making their purchase. Only the initial visit to the study site and the final visit (week 26) were scheduled. Purchasers were informed that they could return to the storefront at any time during the 26-week period to purchase additional medication or a cholesterol test.

Users' behaviors were observed over the possible 26-week treatment period. However, the study was carefully designed not to interfere with or influence self-selection or de-selection decisions. Heart-healthy behavior was evaluated through questionnaires and application of a Meats, Eggs, Dairy, Frying foods, In baked goods, Convenience Foods, Table fats, Snacks (MEDFICTS) dietary assessment. After CUSTOM had concluded, users who exhibited any behavior that required additional clarification were contacted (the Post-CUSTOM Study Clarification Questions). In addition, ~3 months after study completion, 398 users generally representative of the total user population were contacted by telephone for the Post-CUSTOM Survey interview.

A predefined set of behavioral hypotheses was constructed based on results from previous label comprehension testing that indicated that >80% of consumers understood most messages and that >90% understood key safety messages. Based on these results, the behavioral hypothesis benchmarks for users were aggressively set at ≥80% for self-selection and ≥75% for de-selection. Using a conservative and rigorous algorithm that jointly considered all items detailed in the criteria and label directives when assessing behavior, these benchmarks were not achieved with slightly more than one half of the users exhibiting self-selection and de-selection behavior that was consistent with the behavioral hypotheses driven by the highly restrictive label criteria. To fully understand and characterize behavior among all CUSTOM participants (users and nonusers), results are presented item by item into behavioral groupings consistent with ATP III guidelines and described by participants' degree of adherence to the label benefit or safety criteria. Almost all inappropriate behavior was attributable to nonadherence to label benefit criteria and not to safety criteria.

Evaluation criteria: Behavior regarding initial and ongoing use decisions was evaluated in relation to the criteria and directives on the MOTC carton label. It was anticipated that most consumers who met the label criteria would be able to reach their ATP III–defined goal of a LDL cholesterol level of <130 mg/dl with the 20-mg dose of lovastatin. Other parameters used to evaluate the benefits of the MOTC-SMS included the percent change from baseline in LDL cholesterol, percent subjects treated to LDL cholesterol target goal (<130 mg/dl), percent participants who stated that they had discussed high levels of cholesterol and MOTC with their physician, effect of the MOTC-SMS on therapeutic lifestyle changes (diet and exercise habits), overall safety and tolerability, and potential behavioral risk for safety concerns from MOTC. Persistence was defined as percent users who completed ≥24 weeks (168 days) of treatment. Compliance was calculated as the number of tablets taken divided by the number of days users had access to medication.

RESULTS

The flow of participants through the study is presented in Figure 1. The results presented in this report are largely based on the population of evaluators (n = 3,316) and 2 important subpopulations of evaluators, nonpurchasers (n = 2,111) and users (n = 1,061). Two of 1,061 users were identified as protocol violators according to criteria defined in the analysis plan and are excluded from the analysis of behavioral decisions. Safety analyses are based on the complete set of 1,061 users.

TABLE 1 Text of Product Carton Label Tested in the Study*

Use To help lower LDL "bad" cholesterol, which may prevent a first heart attack.

Warnings

Do not use if:

- you have **liver disease**
- you have had any muscle pain, weakness or tenderness from taking a cholesterol-lowering medicine.
- you are **pregnant or breast-feeding**
- you know you are **allergic to lovastatin**

Ask your doctor or pharmacist before use if you are taking:

- any prescription medicine
- other cholesterol-lowering medicine
- new prescriptions:

Do NOT use unless directed by your doctor if you have:

- very high LDL "bad" cholesterol 171–400 mg/dL
- high triglycerides 200–900 mg/dL
- healthy HDL "good" cholesterol 60–200 mg/dL
- diabetes
- ever had heart disease (heart attack or angina)
- had a stroke

Stop use and ask your doctor if you develop any unexplained muscle pain, weakness or tenderness

If you are diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.

How to decide if MEVACOR™ OTC is right for you

Before using you must have:

- Tried a healthy diet and exercise to reduce your cholesterol.
- Had a fasting cholesterol test within the last year.

Who can use; MEVACOR™ OTC is only for:

1. men 45 years or older **AND** women 55 years or older
2. people with LDL "bad" cholesterol between **130–170 mg/dL**
3. people with one or more of these conditions that increase heart disease risk:
   - You are a smoker
   - HDL "good" cholesterol 1–39 mg/dL **(too low)**
   - Heart attack or angina in father or brother before 55; mother or sister before 65 **OR**
   - High blood pressure

Directions

1. **Take one tablet daily:**
   - Continue to eat a healthy diet and exercise.
2. **Test at 6 weeks: See if your LDL test result is below 129 mg/dl: "Yes" or "No"?**
   - No–If at 6 weeks your LDL "bad" cholesterol is higher than 129 mg/dl, stop taking MEVACOR™ OTC. Talk to your doctor. MEVACOR™ OTC may not be enough for you.
   - YES–If at 6 weeks your LDL "bad" cholesterol is below 129 mg/dl, it's working, keep taking it daily and test your cholesterol once a year. If you stop, your cholesterol will go back up.
3. **Talk to your doctor if there is a change in your health:**
   - Tell your doctor you are taking MEVACOR™ OTC before you begin taking any new prescription medicine.
   - If diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.
   - Unexplained muscle pain: Stop use immediately and talk to your doctor if you develop any unexplained muscle pain, weakness or tenderness. This can be a sign of a rare but serious side effect.

*Used with permission of Merck & Co., Inc., West Point, Pennsylvania.

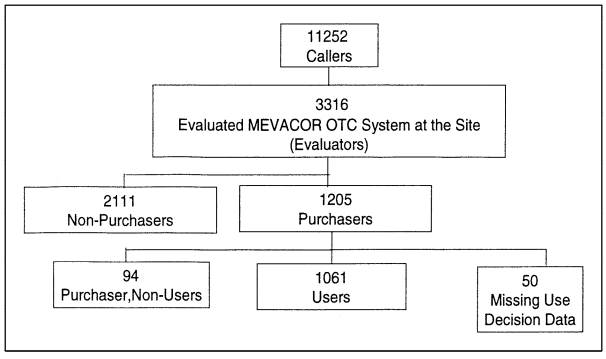

FIGURE 1. Participant flow through the study.

Will the right people use Mevacor OTC? This question addresses the initial decision a consumer makes regarding the use of MOTC (self-selection). Both the nonpurchasers and users provide valuable information regarding this decision.

NONPURCHASERS: Demographic information for this population is presented in Table 2. Most nonpurchasers (98% of those who stated that they were "not interested in buying," 1,673 of 2,111) were ineligible for MOTC by label criteria (Figure 2). Of nonpurchasers, 975 (46%) stated that they needed to talk to their doctor before making a decision to purchase. Further, after returning to the study site for a second visit to reevaluate the product, 471 (22%) reported that they actually *had* spoken to their physician about MOTC. Major reasons for label ineligibility among nonpurchasers included being under age, not knowing one's lipid values, use of a prescription medication, and lacking risk factors for CHD.

USERS: Demographic information for this population is presented in Table 2. Most users were appropriate for therapy by adherence or close adherence to

TABLE 2 Baseline Characteristics of Nonpurchasers and Users

Baseline Characteristics	Nonpurchasers	Users
CUSTOM		
No. of participants	2,111	1,061
Median age (yrs)	51	56
Men	1,226/2,111 (58%)	631/1,061 (60%)
Race		
White	1,401/2,111 (66%)	869/1,061 (82%)
Black	513/2,111 (24%)	90/1,061 (9%)
Hispanic	102/2,111 (5%)	58/1,061 (5%)
Other	95/2,111 (5%)	44/1,061 (4%)
Low literacy	255/2,111 (12%)	136/1,061 (13%)
Did not know LDL cholesterol values at time of self-selection*	732/1,783 (41%)	318/1,034† (31%)
Average baseline LDL cholesterol (mg/dl)	NA	157
≥2 CHD risk factors	904/2,111 (43%)	608/1,061 (57%)
Already tried diet/exercise	NA	820/1,030 (80%)
Discussed cholesterol with physician ≤2 yrs	NA	758/1,030 (74%)
Post-CUSTOM survey		
No. of participants		398
Visit physician ≥2 times/yr (%)	NA	224/398 (56%)
Median household income ($)	NA	43,000
Did not have a drug prescription plan (%)	NA	166/398 (42%)

*Based on subjects' responses to questions on the eligibility assessment.
†Of 318 users who did not know their LDL cholesterol levels at the time of self-selection, 144 (45%) consulted with their physician about taking MOTC.
NA = not available.

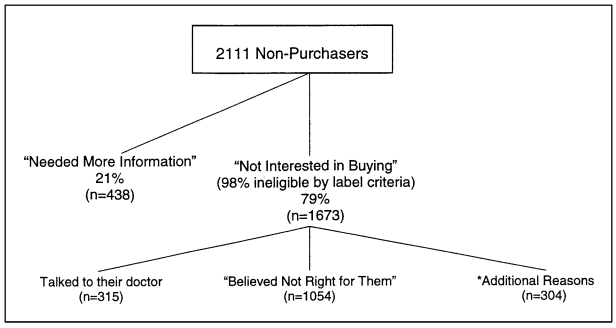

FIGURE 2. Nonpurchaser behavior. *Includes remaining participants who provided (n = 283) or did not provide (n = 21) a reason for deciding not to purchase.

the label benefit criteria (n = 687) or by ATP III guidelines (n = 258). Self-selection behavior was available for analysis from 1,044 users (excluded were 2 who violated the protocol and 15 missing an eligibility assessment). Self-selection behavior is discussed according to those who adhered or closely adhered to the label benefit criteria and those who did not. Users who closely adhered to label benefit criteria met all criteria except for age (too young), lipid values out of range (LDL cholesterol level <130 or >170 mg/dl or high-density lipoprotein cholesterol level ≥60 mg/dl), and not having any risk factors for CHD according to the label. In those instances when users consulted a physician when they did not exactly fit the label criteria, such behavior was classified as adhering to label benefit criteria. Self-reported lipid values (reflecting users' beliefs about their cholesterol health) were used for analysis of behavior.

Users who adhered or closely adhered to the label benefit criteria: of the 1,044 users, 687 (66%) adhered or closely adhered to the label benefit criteria. Recognizing that nonpurchasers are always correct in deciding not to purchase an OTC drug and taking users and nonpurchasers into consideration, 84% of evaluators (n = 3,316) appropriately decided to use MOTC (n = 687) or chose not to purchase the drug (n = 2,111).

Users who did not adhere to the label benefit criteria: of the 1,044 users, 357 did not adhere to the label benefit criteria. Behavior was grouped according to: those who did not know their complete lipid profile (n = 188), those whose self-reported triglyceride levels were ≥200 mg/dl (n = 170), those who substituted MOTC for a prescription lipid-lowering agent (n = 11), and those with high CHD risk (i.e., secondary prevention users and subjects who had diabetes) who did not consult with their physician before starting MOTC (n = 70). Most users who did not adhere to the label benefit criteria (72%; 258 of 357) were eligible for statin therapy according to ATP III. Forty-two percent (151 of 357) were considered to be at intermediate risk for CHD. Among the 70 high CHD risk users who did not consult with their physician before using MOTC, 46 were not on prescription lipid-lowering therapy at the time of self-selection but should have been according to ATP III guidelines. In addition, 26 of these 70 users reported interacting with a physician concerning MOTC later in the study. Therefore, 74% of high CHD risk users (123 of 167) interacted with their physician at some time during the study (97 high CHD risk users consulted with their physician before self-selection and 70 did not).

Can consumers self-manage their cholesterol over time? The MOTC-SMS provides directions for users to self-manage their cholesterol over time. Adherence to the label with respect to self-management of cholesterol was defined as obtaining a follow-up cholesterol test at an interval of 4 to 12 weeks and doing any of the following: achieving the LDL cholesterol target goal of <130 mg/dl and continuing on therapy, not achieving the LDL cholesterol target goal and discontinuing therapy, or not achieving the LDL cholesterol target goal and consulting with a physician. Close adherence was behavior that adhered to these label benefit criteria except that the follow-up test was obtained outside the 4- to 12-week interval.

Of the 1,059 users who were available for behavioral analysis regarding obtaining a follow-up cholesterol test, 116 were not required by the carton label to obtain such a test because they discontinued MOTC

TABLE 3 Interactions With Physicians Regarding Over-the-Counter Mevacor

Group	Interactions With Physician
All evaluators	968/3,316 (29%)
Nonpurchasers*	
Nonpurchasers who declined to purchase because they needed to talk to their physician	975/2,111 (46%)
Nonpurchasers who indicated they had spoken to their physician	471/2,111 (22%)
Nonpurchasers who had LDL cholesterol levels >170 mg/dl or triglyceride levels >200 mg/dl	176/664 (27%)
Purchasers	
Purchasers† before starting MOTC	504/1,205 (42%)
Users*	
All Users	582/1,030 (57%)
High-risk users‡	123/167 (74%)
Users who did not obtain follow-up cholesterol test and spoke with their physician	125/277 (45%)
Users who had been diagnosed with a new medical condition	105/161 (65%)
Users who had been prescribed a new drug	196/270 (73%)
Users who had never talked to their physician about cholesterol or had not done so for >2 yrs	92/269 (34%)

*Subjects may be counted in >1 row.
†Purchasers (n = 1,205) include users (n = 1,061) and purchasers/nonusers (n = 94).
‡High-risk users include those with a history of stroke, diabetes, or CHD.

TABLE 4 Potential Safety Concerns at the Time of Self-Selection

Potential Safety Concern	Evaluators With Condition (n = 764)	Users With Condition (n = 23)
Potential drug interactions		
Nefazodone	6	1
Cyclosporine	3	0
Erythromycin/clarithromycin	10	2
Ketoconazole/itraconazole	2	0
Gemfibrozil	48	2
Niacin (>1,000 mg/d)	57	5
Protease inhibitors	34	1
Reported current liver disease	80	3
Pregnant/breast feeding	12	0
Previous drug allergy to lovastatin	13	0
Use of a prescription cholesterol-lowering medication	609	9

on or before the end of the allowable 4- to 12-week interval. These 116 are not included in the evaluation of ongoing use behavior. Of the remaining 943 users, 666 (71%) did obtain a follow-up test and 277 users did not. Among these 277 users, an end-of-study LDL cholesterol value was available for 201 and it showed that 111 had achieved the LDL cholesterol target goal. For the 666 users who obtained a follow-up test, 499 (75%) exhibited behavior that adhered or closely adhered to the label benefit criteria.

Will users of MOTC achieve beneficial lipid lowering in the OTC setting? Persistence with therapy was 61% (despite the MOTC-SMS discouraging inappropriate users from continuing therapy), and compliance was 75% to 120% for 56% of all users. Although CUSTOM was not primarily designed to evaluate efficacy, most users achieved beneficial modification of their lipid profiles. Among the users who had fasting LDL cholesterol values at baseline and end of study (week 26), a median reduction of 25.2% was observed. The median reduction in LDL cholesterol for all users (fasted and nonfasted) was 20.6%. Of the 878 users who had a known end-of-study LDL cholesterol value, 548 (62%) were at the target goal (LDL cholesterol level <130 mg/dl).

Will consumers involve their physicians in cholesterol self-management? Table 3 lists participant-reported physician interactions during the study. These data suggest that the MOTC-SMS encourages consumers to consult with a health care professional regarding cholesterol management.

Will heart-healthy lifestyle behaviors improve? The MOTC-SMS encourages therapeutic lifestyle changes, such as diet and exercise. Self-reported dietary patterns were improved or maintained in 884 of 903 users (98%), and 364 (40%) reported improvements. In addition, self-reported exercise habits were improved or maintained in 852 of 903 users (94%), and 214 (24%) reported improvements. Based on responses from the MEDFICTS dietary assessment questionnaire, 677 of 820 (82%) users were already on an American Heart Association Step I or II diet at baseline. By study end (week 26), 220 of the 820 users (27%) had further improved their diet: 80 of the 143 users (56%) who had not been on either of the American Heart Association diets progressed to a Step I or II diet, and 140 of the 292 users (48%) who were already on a Step I diet progressed to a Step II diet. At study end, 648 of the 728 users (89%) were on a Step I or II diet.

Can consumers manage potential safety risks? Subpopulations of users with the potential for safety concern at the time of self-selection were categorized according to safety risk groups and included users who had not consulted with a physician and had current liver disease or were potentially at increased risk for statin-associated myopathy. Those potentially at increased risk for statin-associated myopathy included users taking potentially interacting medications and users taking concomitant lipid-lowering therapy. Users who decided to remain on MOTC despite the development of unexplained muscle pain were also potentially at risk for statin-associated myopathy. Based on additional information received from the Post-CUSTOM Clarification Questions, 23 users (2%) at the time of self-selection or during the 26 weeks of therapy (n = 9) exhibited behavior associated with a potential safety concern (Tables 4 and 5).

MOTC was well tolerated over the 26 weeks of the study. Although 452 of 1,061 users (43%) had ≥1 adverse experience, only 180 users (17%) had an adverse experience considered to be drug related by the investigator, and only 125 users (12%) discontin-

TABLE 5 Potential Safety Concerns During the 26-week Study

Potential Safety Concern*	Users With New Events (n = 366)	Users With Suboptimal Behavior (n = 9)
New medical conditions	161	1†
New prescription medications	270	0
Occurrence of unexplained muscle pain	63	8‡

*Users needed to inform their physician that they were using MOTC for new medical conditions and new prescriptions and inform or discontinue the drug due to "unexplained" muscle pain.
†Diabetes.
‡Not recontacted for explanation of behavior.

ued MOTC because of the adverse experience. No users reported being diagnosed by their physician with myopathy, rhabdomyolysis, or acute liver disease. One non–drug-related death occurred (stroke). There was only 1 drug-related serious adverse event, a systemic-type allergic reaction to lovastatin in an patient who had no known allergy to the drug at the time of study initiation.

DISCUSSION

Most approved OTC products are intended for acute symptomatic conditions. In contrast, CUSTOM evaluated the ability of consumers to self-manage a chronic, asymptomatic, potentially lifelong condition without undue risk. CUSTOM tested consumers' approach to self-medication of cholesterol and the extent to which such individuals would adhere to directions incorporated into the labeling, accompanying information, and support materials. An OTC drug-based self-management system does not exist in the United States for any other chronic condition. The MOTC-SMS would be the first such OTC program for consumers, with demonstrated success in discouraging inappropriate consumers from purchasing the product and guiding appropriate individuals to use the drug and self-manage their cholesterol over time. Although CUSTOM was not designed to accurately measure persistence or compliance, the compliance and persistence results with the MOTC-SMS compare favorably with data from the prescription drug setting.[5–10] Cholesterol reduction among users was also consistent with results from randomized, double-blind, placebo-controlled trials.[11–13] Heart-healthy lifestyle behaviors were maintained or improved, indicating that consumers understand that cholesterol self-management extends beyond drug therapy and affects lifestyle habits. Consumers involved their physicians in cholesterol self-management, thus validating the ultimate goal of the MOTC-SMS to establish a collaborative care partnership in the management of cholesterol. The MOTC-SMS directed many cholesterol-concerned individuals into the health care system who may not otherwise have had such physician contact.

OTC self-directed usage of MOTC was well tolerated. Because there was no placebo group in CUSTOM, it was not possible to make a comparison with a background rate for adverse events. However, the safety of 20 mg of lovastatin has been well established in randomized, controlled, clinical trials.[11,12] There were also very few users at potential safety risk at the time of self-selection or during the 26 weeks of therapy. Thus, the data from CUSTOM provide a compelling case for the nonprescription availability of 20 mg of lovastatin. The MOTC-SMS has the potential to contribute to the prevention of CHD in the United States through consumers' self-management of cholesterol and physician collaboration when more aggressive care is indicated.

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Adult Treatment Panel II Versus Adult Treatment Panel III: What Has Changed and Why?

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The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP] III) differs in several ways from the ATP II guidelines. Several principal advances include (1) new risk levels for major lipid measures, (2) increased emphasis on primary prevention, (3) inclusion of high-risk groups in secondary prevention, (4) broader lifestyle program, and (5) increased focus on implementation and adherence. The purpose of this article is to discuss the major changes in ATP III and to highlight the benefits of the new guidelines in the management of hypercholesterolemia in adults.

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Adult Treatment Panel (ATP) III is the latest report in the National Cholesterol Education Program (NCEP) clinical management guidelines for cholesterol testing and management (Table 1). The third ATP report updates the existing recommendations, yet it shares many important features of ATP II. The shared features of ATP III and ATP II include the following: (1) the continued identification of low-density lipoprotein cholesterol (LDL-C) lowering as the primary therapy goal; (2) high levels of LDL-C as the target for LDL-C–lowering drug therapy; (3) intensive LDL-C–lowering therapy for persons with coronary artery disease (CAD); (4) different risk categories for different LDL-C goals; (5) subpopulations to screen for high levels of LDL-C; and (6) emphasis on lifestyle changes, including weight loss and physical activity, to enhance risk reduction (Table 2).[1]

TABLE 1 National Cholesterol Education Program Reports

- Adult Treatment Panel I (1988)
- Recommendations for Improving Cholesterol Measurement (1990)
- Population Strategies for Blood Cholesterol Reduction (1990)
- Blood Cholesterol Levels in Children and Adolescents (1991)
- Adult Treatment Panel II (1993)
- Recommendations on Lipoprotein Measurement (1995)
- Adult Treatment Panel III (2001)

PRINCIPAL ADVANCES

There are several principal advances of ATP III. As outlined in Table 3, the first, and possibly the most critical aspect of the ATP III guidelines, is the focus on the concept of risk. This focus represents a move away from the old concepts of primary and secondary prevention. In ATP III, risk assessment is identified as the first step in risk management. Risk assessment necessitates measurement of LDL-C and identification of accompanying risk determinants.[1] The intensity of risk-reduction therapy should be adjusted to a person's absolute risk as a basic principle of prevention.[1]

Although there are new risk levels for the major lipid measures, there is also an important and broadened emphasis on what has traditionally been called primary prevention. ATP III provides a genuine emphasis on lifestyle programs and includes recommendations that are broader than in previous panel reports. The therapeutic lifestyle change (TLC) program includes: (1) reduction of saturated fat and cholesterol intake, (2) options for enhancing LDL-C lowering with plant stanols/sterols, (3) increased consumption of viscous fiber, (4) weight reduction, and (5) increased physical activity (Table 3).

The ATP III guidelines also focus on the importance of implementation and adherence, because if the guidelines are not implemented, the goals will not be achieved. Key components of implementation and adherence involve a focus on the patient, the physician, and the health-care delivery system. The report describes specific interventions for promoting patient adherence, including: (1) providing explicit patient instruction, (2) use of family support, (3) reinforcing and rewarding adherence, and (4) involving patients in care through self-monitoring.[1] A secondary area of focus for interventions to improve adherence involves the physician and medical office. Some specific interventions include: (1) teaching physicians to implement lipid-treatment guidelines, (2) use of reminders to prompt physicians on lipid management and preventive care, and (3) the use of a standardized treatment plan to structure care.[1] Lastly, interventions focused on the health-care delivery system that can improve adherence include: (1) lipid management through a lipid clinic, (2) use of case management by nurses, and (3) care pathway use.[2]

ATP III also presents modifications of lipid and lipoprotein classification (Table 4). An optimal level of LDL-C defined for the population is a new feature. The new LDL-C optimal goal is <100 mg/dL. The intention is not necessarily to treat all patients to an LDL-C level of <100 mg/dL, but rather, the new

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TABLE 2 Shared Features of Adult Treatment Panels (ATP) III and II

- Continued identification of LDL cholesterol lowering as the primary goal of therapy
- Consideration of high LDL cholesterol (≥160 mg/dL) as a potential target for LDL-lowering drug therapy, specifically as follows:
  - —For persons with multiple risk factors whose LDL levels are high (≥160 mg/dL) after dietary therapy, consideration of drug therapy is recommended.
  - —For persons with 0–1 risk factors, consideration of drug therapy (after dietary therapy) is optional for LDL 160–189 mg/dL and recommended for LDL ≥190 mg/dL.
- Emphasis on intensive LDL-lowering therapy in persons with established CAD
- Identification of 3 categories of risk for different LDL goals and different intensities of LDL-lowering therapy:
  - —CAD and CAD risk equivalents* (other forms of clinical atherosclerotic disease)
  - —Multiple (2+) risk factors†
  - —0–1 risk factor
- Identification of subpopulations, besides middle-aged men, for detection of high LDL cholesterol (and other lipid risk factors) and for clinical intervention. These include:
  - —Young adults
  - —Postmenopausal women
  - —Older persons
- Emphasis on weight loss and physical activity to enhance risk reduction in persons with elevated LDL cholesterol

CAD = coronary artery disease; LDL = low-density lipoprotein.

*A CAD risk equivalent is a condition that carries an absolute risk for developing new CAD equal to the risk for having recurrent CAD events in persons with established CAD.

†Risk factors that continue to modify the LDL goal include cigarette smoking, hypertension, low high-density lipoprotein cholesterol, family history of premature CAD, age (men ≥45 years and women ≥55 years), and diabetes (in ATP III diabetes is regarded as a CAD risk equivalent).

Adapted from *JAMA*.[1]

TABLE 3 Principal Advances of National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)

- New risk levels for major lipid measures (LDL-C, HDL-C, triglycerides)
- Increased emphasis on primary prevention
- Inclusion of high-risk groups in secondary prevention
- Broader lifestyle program and recommendations, eg, TLC:
  - —Reduced intakes of saturated fats (<7% of total calories) and cholesterol (<200 mg/day)
  - —Therapeutic options for enhancing LDL lowering such as plant stanols/sterols (2 g/day) and increased viscous (soluble) fiber (10–25 g/day)
  - —Weight reduction
  - —Increased physical activity
- Focus on implementation and adherence

HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; TLC = therapeutic lifestyle changes.

Adapted from *JAMA*.[1]

optimal goal is a statement about what is "optimal" for our population.

EMPHASIS ON PREVENTION AND RISK ASSESSMENT

The emphasis on primary prevention focuses on both short-term and long-term risk. Although ATP III emphasizes calculation of short-term or 10-year risk, there is an important discussion of long-term lifetime risk. Calculating short-term risk involves use of the global risk score based on information derived from the Framingham Heart Study. The rationale for using the risk score is that it allows us to match the intensity of therapy with the level of risk. In addition, use of risk scoring has proven to be valid and easy to use, and has been successfully adopted by European cardiology societies. Furthermore, the use of risk scoring is a key motivational tool, not only for patients, but also for providers.

Access to the Framingham global risk scoring system is quite easy. A hardcopy version is part of the ATP III executive summary.[1] It is also available on the National Heart, Lung, and Blood Institute's Web site.[3] The American Heart Association also has a version of it on its Web site.[4] There is a format that can be downloaded for use with computers and Palm Pilot (Palm Inc., Santa Clara, CA) devices. A key ATP III strategy emphasizes that, for patients with multiple (≥2) risk factors, a 10-year risk assessment should be performed. Although a 10-year risk assessment can be performed for everyone, it is only optional for general population primary prevention screening. It is required in ATP III for patients with ≥2 risk factors. For patients with 0 to 1 risk factors, the 10-year risk assessment is not required, because most patients have <10%, 10-year risk.

A subtle, but important distinction between ATP II

TABLE 4 Modification of Lipid and Lipoprotein Classification

- LDL cholesterol <100 mg/dL = optimal
- HDL cholesterol <40 mg/dL
  - —Categorical risk factor
  - —Raised from <35 mg/dL
- Lower triglyceride classification cut points
  - —More attention to moderate elevations

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

TABLE 5 Low-Density Lipoprotein (LDL) Cholesterol Goals and Cut Points for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate TLC (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CAD or CAD risk equivalents (10-yr risk >20%)	<100	≥100	≥130 (100–129; drug optional)
≥2 risk factors (10-yr risk ≤20%)	<130	≥130	10-yr risk 10%–20%; ≥130 10-yr risk <10%; ≥160
0–1 risk factor	<160	≥160	≥190 (160–189; LDL-lowering drug optional)

CAD = coronary artery disease.
Adapted from *JAMA*.[1]

and ATP III is the LDL-C goal for high-risk patients. ATP II specified an LDL-C goal of ≤100 mg/dL. In ATP III, the LDL-C goal is now <100 mg/dL. Table 5 outlines the LDL-C goals and cut points for TLC and drug therapy in different risk categories.

HIGH-RISK GROUPS IN ADULT TREATMENT PANEL III

Another critical area that is new in ATP III guidelines is the designation of other high-risk groups for secondary prevention, known as CAD risk equivalents. The categories of CAD risk equivalents include: (1) patients with clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease), (2) diabetes, and (3) patients who have a 10-year CAD risk score >20%. Diabetes now counts as a CAD risk equivalent, because the 10-year risk for CAD in asymptomatic patients with diabetes is about 20% for having a coronary disease event. Diabetes is also associated with a higher rate of mortality once CAD develops, including a high rate of mortality with acute myocardial infarction and after acute myocardial infarction.

METABOLIC SYNDROME

The metabolic syndrome is a constellation of important major risk factors that include life-habit risk factors and newer or emerging risk factors. It is increasingly prevalent in the United States because of a variety of factors, including an increase in calories in our diet and physical inactivity. It has a clear impact on CAD risk and it is treatable. The general features of the metabolic syndrome are outlined in Table 6. ATP III has developed a standard definition for the metabolic syndrome as well (Table 7). Although some will argue that there are other elements of the metabolic syndrome that may be important, this definition, based on having ≥3 of these 5 factors, is easy for clinicians to use. Being able to define the metabolic syndrome also allows clinicians to focus on this concept as a diagnostic syndrome of clinical importance.

The therapeutic objectives for treating the metabolic syndrome are (1) to reduce underlying causes, in particular, obesity and physical inactivity; (2) to treat associated lipid and nonlipid risk factors, including hypertension; (3) use of aspirin in patients with CAD to reduce the prothrombotic state; and (4) treatment of atherogenic dyslipidemia (lipid triad). Although it is not yet clear precisely what the level of risk is for an individual with a metabolic syndrome, we do know that treatment is effective at reducing that risk.

HIGH-DENSITY LIPOPROTEIN CHOLESTEROL IN ADULT TREATMENT PANEL III

There are 3 key points in ATP III involving high-density lipoprotein cholesterol (HDL-C): (1) There is a new cut point for an abnormal or low HDL-C level. "Low" HDL-C has moved from <35 mg/dL to <40 mg/dL in ATP III. (2) There are 2 different cut points, based on sex, to qualify for the diagnosis of the metabolic syndrome (men, HDL-C <40 mg/dL; women, HDL-C <50 mg/dL). (3) The current evidence is insufficient to specify an exact goal for therapy, thus there is no specific HDL-C target. When discussing management of low HDL-C levels, the causes of low HDL-C need to be considered (Table 8). However, it remains important to remember that LDL-C is the primary target.

Recommendations for weight reduction and increased physical activity should be followed because

TABLE 6 Metabolic Syndrome: General Features

- Abdominal obesity
- Atherogenic dyslipidemia
  - —Elevated triglycerides
  - —Small LDL particles
  - —Low HDL cholesterol
- Raised blood pressure
- Insulin resistance (±glucose intolerance)
- Prothrombotic state
- Proinflammatory state

Synonyms:

- Insulin resistance syndrome
- (Metabolic) syndrome X
- Dysmetabolic syndrome
- Multiple metabolic syndrome

HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol.

TABLE 7 Diagnosis of the Metabolic Syndrome*

- Abdominal obesity (waist circumference):
  - —Men ≥103 cm (40 in)
  - —Women ≥88 cm (35 in)
- Triglycerides: ≥150 mg/dL
- HDL cholesterol:
  - —Men <40 mg/dL
  - —Women <50 mg/dL
- Blood pressure: ≥130/≥85 mm Hg
- Fasting serum glucose: ≥110 mg/dL

HDL = high-density lipoprotein.
*Diagnosis based on having ≥3 of the 5 factors listed.

TABLE 8 Causes of Low High-Density Lipoprotein Cholesterol

- Elevated triglycerides
- Overweight and obesity
- Physical inactivity
- Type 2 diabetes
- Cigarette smoking
- Very high carbohydrate intakes (>60% energy)
- Certain drugs (β-blockers, anabolic steroids, progestational agents)

both will decrease risk as well as increase levels of HDL-C. Non–HDL-C is a secondary target of therapy if triglycerides are >200 mg/dL. Nicotinic acid or fibrates should also be considered for patients with low levels of HDL-C, particularly for those with CAD or CAD risk equivalents.

FROM DIET STEPS TO THERAPEUTIC LIFESTYLE CHANGE

A last area of differentiation between ATP II and ATP III is related to the movement from the stepped-care diet program in ATP II, to the broader lifestyle change emphasis in ATP III. Lifestyle change is more than simply diet change, and a broader focus was necessary for our diverse population. The importance of saturated fat versus total fat has led to some confusion and perhaps, some inappropriate advice over the years. In fact, an increase in caloric intake from popular "low-fat" food products and snacks is partly the result of an excessive focus on low fat. The importance of the role of monounsaturated and polyunsaturated fatty acids, particularly for HDL-C and triglycerides, is clear. The importance of calories versus the components also needed to be emphasized. Finally, the importance of physical activity is highlighted in ATP III.

The challenge of implementation and adherence is clear. The science of implementation and adherence has advanced considerably in the last 10 to 15 years. There is an incredibly rich base of evidence for behavioral change, and ATP III has included evidenced-based adherence recommendations embedded on this science. New tools are also available to help promote the implementation of the ATP III guidelines. NCEP resources to foster ATP III implementation include the following: (1) the Executive Summary[1]; (2) ATP III At-A-Glance: Quick Desk Reference[5]; and (3) Web-based and electronic tools, including the Palm OS interactive tool for use at point of care, the 10-year risk calculator, and PowerPoint (Microsoft Corp., Redmond, WA) slide set for teaching purposes. Several resources are specifically for the patient, to foster implementation and adherence. These include the *Live Healthier, Live Longer* Web site[6] and the NCEP patient brochure *High Blood Cholesterol: What You Need to Know*.[7] The 10-year risk calculator results can also be shared with patients to visually depict how their CAD risk can be affected by their adherence.

Knowledge of the changes in ATP II and the rationale for change is important in promoting understanding of the new ATP III guidelines as well as in achieving them. These are evidenced-based changes and reflect advances in our knowledge of factors that affect CAD risk as well as the effects of various aspects of treatment in reducing CAD risk. ATP III builds on ATP II with the purpose of reaching the ultimate goal in the management of hypercholesterolemia: the reduction of CAD risk, morbidity, and mortality associated with CAD.

CONCLUSION

ATP III is the latest of NCEP's clinical management guidelines for high levels of blood cholesterol in adults. Although ATP II and ATP III share many important features, new features of ATP III—including a focus on the concept of risk, new LDL-C goals, intensive LDL-C–lowering therapy for persons with CAD, and emphasis on lifestyle changes—all have the potential to significantly affect CAD risk reduction. As with previous guidelines, implementation and adherence are key components in ensuring that CAD risk reduction is ultimately achieved.

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ACC/AHA/NHLBI CLINICAL ADVISORY ON STATINS

ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins

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PREAMBLE

The voluntary withdrawal of cerivastatin (Baycol) from the U.S. market on August 8, 2001, by the manufacturer, in agreement with the Food and Drug Administration (FDA), has prompted concern on the part of physicians and patients regarding the safety of the cholesterol-lowering class of drugs called HMG CoA reductase inhibitors, more commonly known as "statins." This American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute (ACC/AHA/NHLBI) Clinical Advisory is intended to summarize for professionals the current understanding of statin use, *focused on myopathy*, and to provide updated recommendations for the appropriate use of statins, including cautions, contraindications, and safety monitoring for statin therapy. Its purpose is not to discourage the appropriate use of statins, which have life-saving potential in properly selected patients, particularly those with established coronary heart disease (CHD) and others at high risk for developing CHD. Included are recent myopathy information compiled by the FDA, information from clinical trials, and summaries from the recently released report of the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) (1).

INTRODUCTION

In the literature, the general terminology used to describe muscle toxicity is inconsistent. Therefore, for the purpose of this document, the following terms are used as defined here: *Myopathy*—a general term referring to any disease of muscles; myopathies can be acquired or inherited and can occur at birth or later in life (Source: NINDS Myopathy Page-http://accessible.ninds.nih.gov/health_and_medical/disorders/myopathy.htm). *Myalgia*—muscle ache or weakness without creatine kinase (CK) elevation. *Myositis*—muscle symptoms with increased CK levels. *Rhabdomyolysis*—muscle symptoms with marked CK elevation (typically substantially greater than 10 times the upper limit of normal [ULN]) and with creatinine elevation (usually with brown urine and urinary myoglobin).

Statins are powerful low-density lipoprotein (LDL)-lowering drugs that are widely used in clinical practice. Results from clinical trials with a mean duration of 5.4 years have demonstrated a decrease in CHD and total mortality, reductions in myocardial infarctions, revascularization procedures, stroke, and peripheral vascular disease (2–8). These trials documented a benefit in both men and women, primarily in middle-aged and older persons treated in the setting of either primary or secondary prevention. More than 50,000 individuals have been randomized to either a placebo or statin in these trials, and no serious morbidity or

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increase in mortality was observed in the drug treatment groups. These agents reduce the risk of essentially every clinical manifestation of the atherosclerotic process; they are easy to administer, with good patient acceptance. There are very few drug to drug interactions. Although the experience with the safety of statin therapy outside of clinical trials has not been fully reported, it is reasonable to suspect that the incidence of side effects may be higher in clinical situations where patients are not monitored as closely as they are in clinical trials (9).

The NCEP has published updated guidelines for treatment of high blood cholesterol (Adult Treatment Panel III report) (1). These guidelines are endorsed by the ACC and AHA. They identify elevated LDL cholesterol as the primary target of therapy and establish goals for LDL cholesterol that depend on a patient's risk status. The Adult Treatment Panel III report was able to apply rigorous clinical trial evidence to identify additional high-risk individuals for treatment, greatly expanding the number of patients who are candidates for these drugs. These include patients with established CHD, other forms of atherosclerotic disease, diabetes mellitus, multiple risk factors imparting high risk, and severe hypercholesterolemia. In many patients, relatively high doses of statins will be required to achieve LDL cholesterol goals of therapy. In addition, for patients with high triglycerides, non–high-density lipoprotein (HDL) cholesterol (LDL + VLDL [very low density lipoprotein] cholesterol) has been identified as a secondary target of therapy. To achieve the non–HDL cholesterol goal, many patients will require statin therapy as well. This broad expansion of statin use will require that increased attention be given to every aspect of statin therapy (i.e., efficacy, safety, and cost-effectiveness).

In view of the demonstrated safety of these agents, both medical professionals and the public were surprised by the recent withdrawal of a relatively new statin, cerivastatin (Baycol), from the market. Cerivastatin was first approved for use in the U.S. in 1997. In August 2001, the manufacturer, Bayer AG, announced the withdrawal of all dosages of its cholesterol-lowering drug with the brand names Baycol/Lipobay (cerivastatin) because of increasingly frequent reports of serious myopathy, including severe and life-threatening rhabdomyolysis. Rhabdomyolysis was reported most frequently when cerivastatin was used at higher doses and, particularly, in combination with another lipid-lowering drug, gemfibrozil (LOPID and generics). At the time of withdrawal, the FDA had received reports of 31 U.S. deaths due to severe rhabdomyolysis associated with the use of cerivastatin, 12 of which involved concomitant gemfibrozil use (http://www.fda.gov/cder/drug/infopage/baycol/). Subsequently, the Wall Street Journal (1/21/02, pg. A10) reported that Bayer AG had indicated that as many as 100 deaths have been linked to Baycol. The FDA reports that the rate of fatal rhabdomyolysis is 16 to 80 times more frequent for cerivastatin as compared to any other statin (10).

INCIDENCE OF ADVERSE EVENTS

The statins are well tolerated by most persons. Elevated hepatic transaminases generally occur in 0.5% to 2.0% of cases and are dose-dependent (11,12). Whether transaminase elevation with statin therapy constitutes true hepatotoxicity has not been determined. Progression to liver failure specifically due to statins is exceedingly rare if it ever occurs (13). Reversal of transaminase elevation is frequently noted with a reduction in dose, and elevations do not often recur with either re-challenge or selection of another statin (14,15). Cholestasis and active liver disease are listed as contraindications to statin use; however, no specific evidence exists showing exacerbation of liver disease by statins. Furthermore, statins have not been shown to worsen the outcome in persons with chronic transaminase elevations due to hepatitis B or C, and treatment of hyperlipidemia may actually improve transaminase elevations in individuals with fatty liver (16). An observational study (16a) has suggested a rare association of statin use with polyneuropathy. This has not been found in the large blinded randomized controlled trials.

The ability of statins to produce myopathy under some circumstances is well established. A common complaint is non-specific muscle aches or joint pains that are generally not associated with significant increases in creatine kinase. In placebo-controlled trials, the incidence of these complaints (generally reported as about 5%) is similar between placebo and active drug therapy, suggesting they may not be drug-related (12–17). Nonetheless, in some patients, the temporal association with statin therapy is strong enough to implicate these drugs as a cause of these complaints. Other patients can have mild-to-moderate elevations of creatine kinase without muscle complaints. Again, elevations may be non-specific, but a statin effect often cannot be ruled out.

It is rare that patients treated with a statin exhibit severe myositis characterized by muscle aches, soreness or weakness and associated with elevated creatine kinase levels, generally greater than 10 times the ULN. In this setting, failure to discontinue drug therapy can lead to rhabdomyolysis, myoglobinuria, and acute renal necrosis (18). Myositis is most likely to occur in persons who have complex medical problems and/or who are taking multiple medications. It may rarely occur with statin monotherapy, but it occurs more frequently when statins are used in combination with a variety of medications, including cyclosporine, fibrates, macrolide antibiotics, certain antifungal drugs, and niacin (19–21). Some of the drug to drug interactions involve specific interactions with the cytochrome P-450 drug-metabolizing system, especially those involving the 3A4 isozyme (22,23). The combination of statins with a fibrate is attractive for persons who have both high serum cholesterol and high triglycerides or for those who continue to have elevated triglycerides after reaching their LDL-cholesterol target on statin therapy. However, there may be a concern about an increased danger of developing myop-

athy with this combination. In the past, this combination was thought to be "contraindicated" because of the potential danger of myopathy. More recently, it has been used increasingly with apparent safety in the majority of persons. This combination is now presented by the ATP III report as an option, with careful monitoring, for some forms of dyslipidemia.

The FDA report comparing the rate of fatal rhabdomyolsis among different statins is of considerable importance (10). The FDA performed a detailed review of all reports of fatal rhabdomyolysis in their Adverse Event Reporting System and obtained the number of prescriptions dispensed since marketing of each statin began in the U.S. Fatal rhabdomyolysis was extremely rare (less than 1 death/million prescriptions). As previously noted, the rate of fatal rhabdomyolsis for cerivastatin was far greater than that for other statins (16 to 80 times higher). Even after excluding cases in which cerivastatin was administered with gemfibrozil, the reporting rate for fatal rhabdomyolysis with cerivastatin *monotherapy* (1.9 deaths per million prescriptions) was 10 to 50 times higher than for other statins. The FDA report also noted that more than 60% of the fatal cases with cerivastain were associated with use of the highest dose (0.8 mg daily). The FDA notes that the data are reporting rates, *not* incidence rates. Thus, statistically "rigorous comparisons between drugs . . . are not recommended" (10). Nevertheless, review of these data strongly suggests that there were no clinically important differences in the rate of fatal complications among the five statins now available in the U.S. (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin). Clinicians should consider the rates of severe myopathy as equivalent among all of these approved statins.

The following are summary comments reflecting current experience with these issues:

- Statin therapy appears to carry a small but definite risk of myopathy when used alone. According to several large clinical trial databases, the incidence of severe myopathy is reported to be 0.08% with lovastatin and simvastatin (14,15). Elevations of CK greater than 10 times the ULN have been reported in 0.09% of persons treated with pravastatin. All currently marketed statins appear to have a similar potential for causing this adverse effect.
- Fibrate treatment alone appears to be associated with some (probably similar) risk of myopathy.
- Of the nearly 600 persons who have participated in controlled clinical trials of a statin and fibrate combination, 1% have experienced a CK greater than 3 times the ULN without muscle symptoms, and 1% have been withdrawn from therapy because of muscle discomfort (24–31). None of these findings were considered serious by the trial investigators. No cases of rhabdomyolysis or myoglobinuria have been encountered in these clinical trials. The experience in these trials is predominantly with lovastatin and gemfibrozil, but it is reasonable to believe that the experiences with other statin-fibrate combinations would be similar.

MECHANISM OF MYOPATHY

Because it occurs so rarely, little is known about the fundamental mechanisms of statin-associated myopathy. It has been suggested that statins lead to inhibited synthesis of compounds arising from the synthetic pathway of cholesterol. In theory, this could lead to ubiquinone (an essential intracellular energy component) deficiency in muscle cell mitochondria, disturbing normal cellular respiration and causing adverse effects including rhabdomyolysis. Despite in-vitro support for this concept (32,33), a human study of six months of simvastatin treatment (20 mg per day) on skeletal muscle concentrations of high-energy phosphates and ubiquinone demonstrated that the muscle high-energy phosphate and ubiquinone concentrations assayed after simvastatin treatment were similar to those observed at baseline and did not differ from values in control subjects (34). No clinical study has yet provided support for the hypothesis of diminished isoprenoid synthesis or energy generation in muscle cells during statin therapy. Some have proposed that statin interaction with the cytochrome P-450 hepatic enzyme system might be related to myopathy (22). Support for this concept comes, in part, from the known enhanced toxicity when statins are administered with agents sharing metabolism by the same cytochrome isoforms. Finally, it has been shown that exercise in combination with lovastatin produces greater creatine kinase elevations than those produced by exercise alone, suggesting that statins can exacerbate exercise-induced skeletal muscle injury (35).

DIAGNOSIS

Routine laboratory monitoring of CK is of little value in the absence of clinical signs or symptoms. Therefore, all persons beginning to receive statins should be instructed to report muscle discomfort or weakness or brown urine immediately, which should then prompt a CK measurement.

MANAGEMENT

Baseline Measurements

Before initiating statin therapy, baseline measurements, including a lipid and lipoprotein profile, that will be used to follow the drug's efficacy and safety should be documented. Current labeling for all statins requires baseline measurements of liver function, including alanine transferase and aspartate transferase, although this is not agreed on by many liver experts and will likely undergo review in the future. Modest transaminase elevations (less than 3 times the ULN) are not thought to represent a contraindication to initiating, continuing, or advancing statin therapy, as long as patients are carefully monitored. Many experts also favor,

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and the ATP III report recommends, baseline CK measurement, reasoning that asymptomatic CK elevations are common and pre-treatment knowledge of this condition can aid in later clinical decision making.

Monitoring for Adverse Reactions and Adjusting Therapy

Once therapy has been initiated, symptoms may appear at any time. If myositis is present or strongly suspected, the statin should be discontinued immediately. Several key points should be kept in mind.

Obtain a CK measurement if the patient reports suggestive muscle symptoms, and compare to CK blood level prior to beginning therapy. Because hypothyroidism predisposes to myopathy, a thyroid-stimulating hormone level should also be obtained in any patient with muscle symptoms.

If the patient experiences muscle soreness, tenderness, or pain, with or without CK elevations, rule out common causes such as exercise or strenuous work. Advise moderation in activity for persons who experience these symptoms during combination therapy.

Discontinue statin therapy (or statin *and* niacin or fibrate if the patient is on combination therapy) if a CK greater than 10 times the ULN is encountered in a patient with muscle soreness, tenderness, or pain.

If the patient experiences muscle soreness, tenderness, or pain with either no CK elevation or a moderate elevation (3 to 10 times the ULN), follow the patient's symptoms and CK levels weekly until there is no longer medical concern or symptoms worsen to the situation described previously (at which point therapy should be discontinued). For patients who develop muscle discomfort and/or weakness and who also have progressive elevations of CK on serial measurements, either a reduction of statin dose or a temporary discontinuation may be prudent. A decision can then be made whether or when to reinstitute statin therapy.

Asymptomatic Patients With CK Elevation

Prior to the withdrawal of cerivastatin, the ATP III report did not recommend routine ongoing monitoring of CK in asymptomatic patients. If a physician chooses to obtain CK values in asymptomatic patients, particularly those on combination therapy, and CKs are elevated to more than 10 times the ULN, strong consideration should be given to stopping therapy. Following discontinuation, wait for symptoms to resolve and CK levels to return to normal before reinitiating therapy with either drug and use a lower dose of the drug(s) if possible.

Some asymptomatic patients will have moderate (i.e., between 3 and 10 times the ULN) CK elevations at baseline, during treatment, or after a drug holiday. Such patients can usually be treated with a statin without harm. However, particularly careful monitoring of symptoms and more frequent CK measurements are indicated.

PREVENTION

Increased Risk States for Statin-Associated Myopathy

Prevention of statin-associated myopathy can best be accomplished by attention to those factors that might increase the risk for such myopathy:

- Advanced age (especially more than 80 years) in patients (women more than men)
- Small body frame and frailty
- Multisystem disease (e.g., chronic renal insufficiency, especially due to diabetes)
- Multiple medications
- Perioperative periods
- Specific concomitant medications or consumption as listed below (check specific statin package insert for warnings)
  - Fibrates (especially gemfibrozil, but other fibrates too)
  - Nicotinic acid (rarely)
  - Cyclosporine
  - Azole antifungals
  - Itraconazole and ketoconazole
  - Macrolide antibiotics
  - Erythromycin and clarithromycin
  - HIV protease inhibitors
  - Nefazodone (antidepressant)
  - Verapamil
  - Amiodarone
  - Large quantities of grapefruit juice (usually more than 1 quart per day)
  - Alcohol abuse (independently predisposes to myopathy)

Clinical Precautions

Most myopathy associated with statins appears to occur in patients who are at risk for the condition. For this reason, physicians should be aware of several caveats when prescribing statin therapy. Myopathy is more likely to occur at higher statin doses than at lower doses. For this reason, doses should not exceed those required to attain the ATP III goal of therapy. As a rule, statin therapy should be employed more cautiously in older persons, particularly older thin or frail women, but it is not contraindicated in these or other high-risk patients. Among older persons, those with multisystem disease apparently are at higher risk. Patients with diabetes combined with chronic renal failure also appear to be at higher risk for myopathy—such patients should be monitored carefully. In several instances, myopathy has developed when patients were continued on statin therapy during hospitalization for major surgery. Therefore, it probably is prudent to withhold statins during such periods.

Particular attention should be given to drug interactions when employing statin therapy. Although the combination of statin plus fibrate is accompanied by an increased danger of myopathy, the use of moderate statin doses combined

Table 1. Summary of HMG CoA Reductase Inhibitors

Available drugs	Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin
Lipid/lipoprotein effects	LDL cholesterol ↓ 18–55 percent HDL cholesterol ↑ 5–15 percent Triglycerides ↓ 7–30 percent
Major use	To lower LDL-cholesterol
Contraindications	
Absolute	Active or chronic liver disease
Relative	Concomitant use of cyclosporine, gemfibrozil, or niacin, macrolide antibiotics, various anti-fungal agents, and cytochrome P-450 inhibitors
Efficacy	Reduce risk for CHD and stroke
Safety	Side effects minimal in clinical trials
Usual starting dose	Lovastatin - 20 mg Pravastatin - 20 mg Simvastatin - 20 mg Fluvastatin - 20 mg Atorvastatin - 10 mg
Maximum FDA-approved dose	Lovastatin - 80 mg Pravastatin - 80 mg Simvastatin - 80 mg Fluvastatin - 80 mg Atorvastatin - 80 mg
Available preparations	Lovastatin - 10, 20, 40 mg tablets Pravastatin - 10, 20, 40, 80 mg tablets Simvastatin - 5, 10, 20, 40, 80 mg tablets Fluvastatin - 20, 40, 80 (xl) mg tablets Atorvastatin - 10, 20, 40, 80 mg tablets

with fibrate appears to have a relatively low incidence of myopathy, especially when used in persons without multisystem disease or multiple medications. The combination of statin plus nicotinic acid seemingly carries a lower risk for myopathy than does statin plus fibrate. Finally, physicians should be aware of the dangers of interactions of statins with the other drugs previously listed. These combinations should also be used with caution or avoided altogether. Furthermore, it is important for clinicians prescribing statins to make sure that their patients are aware of these potential drug interactions, because in current practice, a patient may receive prescriptions from many different caregivers.

Table 2. Monitoring Parameters and Follow-Up Schedule

	Monitoring Parameters	Follow-Up Schedule
Statins	Headache, dyspepsia	Evaluate symptoms initially, 6 to 8 weeks after starting therapy, then at each follow-up visit
	Muscle soreness, tenderness, or pain	Evaluate muscle symptoms and CK before starting therapy. Evaluate muscle symptoms 6 to 12 weeks after starting therapy and at each follow-up visit. Obtain a CK measurement when persons have muscle soreness, tenderness, or pain.
	ALT, AST	Evaluate ALT/AST initially, approximately 12 weeks after starting therapy, then annually or more frequently if indicated.

ALT = alanine transferase; and AST = aspartate transferase.

SUMMARY

Statin therapy holds great promise for reducing the incidence of major coronary events, coronary procedures, and stroke in high-risk patients. At present, this potential has not been fully realized, because many patients at heightened risk are not being treated with these drugs. There is a well documented under-use of statins in clinical practice. Statins have proven to be extremely safe in the vast majority of patients receiving them. Few significant side effects were observed in clinical trials, and post-marketing reports of adverse events have been very limited when considered in comparison to the very large number of persons safely receiving these drugs. Even so, these drugs are not *entirely free* of side effects, and as for all drugs, they should be used appropriately and judiciously. This advisory encourages the appropriate use of statins while pointing out the possibility of side effects in certain patients. If statins are used with appropriate caution in these selected patients, the likelihood of developing clinically important myopathy should be substantially reduced. (See Tables 1 and 2.)

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Expanding Primary Prevention Efforts: Allowing Consumers Access to Over-the-Counter Statins

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CME Issue

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Expanding Primary Prevention Efforts: Allowing Consumers Access to Over-the-Counter Statins

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This supplement to the American Journal of Cardiology contains references to off-label/unapproved uses of medications. The supplement focuses on over-the-counter statins, which have not been granted over-the-counter status by the United States Food and Drug Administration (FDA). The supplement also discusses the need for liver function test monitoring with statins. The prescribing information for statins recommends that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation of dose, and periodically (e.g., semiannually) thereafter. The opinions expressed in this presentation are those of the panelists and are not attributable to the sponsor or the publisher, editor, or editorial board of The American Journal of Cardiology. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. References made in the articles may indicate uses of drugs at dosages, for periods of time, and in combinations not included in the current prescribing information.

Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

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EXPANDING PRIMARY PREVENTION EFFORTS: ALLOWING CONSUMERS ACCESS TO OVER-THE-COUNTER STATINS

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CME INFORMATION

Expanding Primary Prevention Efforts: Allowing Consumers Access to Over-the-Counter Statins

Educational Objectives

After reviewing this supplement, participants will be able to:

- Describe the current trends in the management of cholesterol levels among United States adults
- Identify the current cholesterol treatment gap
- Understand results of the National Lipid Association survey regarding physician and consumer attitudes about cholesterol management and over-the-counter statins
- Assess consumers' ability to safely and effectively self-manage their cholesterol levels
- Evaluate the need for liver function tests and creatine phosphokinase monitoring with statins
- Discuss the approval of over-the-counter statins in the United Kingdom

Target Audience

This program has been developed for physicians and other healthcare providers concerned with primary prevention and lipid management.

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This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Elsevier Office of Continuing Medical Education and The Resource Group. The Elsevier Office of Continuing Medical Education is accredited by the ACCME to provide continuing medical education for physicians.

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This program is supported by an unrestricted educational grant from Johnson & Johnson-Merck Consumer Pharmaceuticals Co.

Disclosure

This supplement to the American Journal of Cardiology contains references to off-label/unapproved uses of medications. The supplement focuses on over-the-counter statins, which have not been granted over-the-counter status by the United States Food and Drug Administration (FDA). The supplement also discusses the need for liver function test monitoring with statins. The prescribing information for statins recommends that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation of dose, and periodically (e.g., semiannually) thereafter.

Expanding Primary Prevention Efforts: Allowing Consumers Access to Over-the-Counter Statins

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The American Journal of Cardiology

Introduction

Thomas A. Pearson, MD, PhD, MPH

Based on evidence from the basic sciences, epidemiologic studies, and clinical trials, hypercholesterolemia is well established as a major risk factor for atherosclerotic cardiovascular disease. An exciting development over the past 2 decades has been the identification and evaluation of increasingly effective pharmaceutical interventions to beneficially modify the lipoprotein profile. A rich database from randomized trials using anatomic and clinical end points has resulted in the organization of the National Cholesterol Education Program (NCEP) and the issuance of 3 reports from its Adult Treatment Panels (ATPs) in 1989, 1993, and 2001.[1–3] These guidelines emphasize the effectiveness of reduction in low-density lipoprotein (LDL) cholesterol through therapeutic lifestyle changes (diet, exercise, weight control) and, in persons with moderate or high risk of coronary artery disease (CAD), pharmacologic interventions to prevent either initial or recurrent myocardial infarction (MI), cardiac death, and a host of other clinical end points.[3] The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, or statins, have rightfully emerged as the most commonly prescribed first-line drug therapy based on their LDL-lowering potency and their efficacy and safety as shown in numerous clinical trials.

However, this large and convincing database on statin efficacy and safety has not been fully appreciated. The resulting treatment gap (ie, the difference between treatment as recommended by guidelines and that actually received) has been well documented. This treatment gap has prompted a discussion of making statins available over the counter (OTC) as a means to improve access to this class of medicines for persons at moderate risk (10% to 20% over 10 years) of CAD in the primary prevention setting.

Initial discussions of the topic were published in 2000 in another supplement to *The American Journal of Cardiology*.[4] Dr. Sidney C. Smith, Jr., reviewed the treatment gap as quantified in the late 1990s and described the status of OTC treatments then in use for the prevention of CAD.[5] The implications of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a randomized clinical trial of lovastatin in moderate-risk subjects for primary prevention of CAD, was discussed by Dr. Antonio M. Gotto, Jr.[6] In a subset of AFCAPS/TexCAPS patients who would be eligible for nonprescription lovastatin, a post hoc analysis documented a statistically significant 44% relative risk reduction in nonfatal MI, unstable angina, and fatal CAD. This trial remains one of the most relevant demonstrations of efficacy and safety in a population in which 83% of subjects would not have otherwise been eligible for drug therapy according to NCEP ATP II guidelines.[2] The safety of statins in terms of hepatotoxicity was reviewed by Dr. Keith G. Tolman,[7] including animal toxicology studies and results of clinical trials in human subjects. The safety of statins was emphasized along with the futility of monitoring to detect serious adverse reactions. Finally, I examined the benefits of populationwide cholesterol reduction from epidemiologic, economic, and ethical perspectives using results from the National Health and Nutrition Examination Survey (NHANES) from 1988 to 1994.[8] The role of populationwide cholesterol reduction as a cornerstone of any program to reduce the burden of CAD was emphasized.

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The present supplement provides updated evidence regarding issues relevant to the use of OTC statins as an approach to risk reduction in individuals at moderate risk of CAD who are currently ineligible for prescription statin therapy. First, the continuing need for new strategies to reduce populationwide cholesterol levels is revisited. The epidemiology of CAD mortality and incidence during the 1990s showed a slowing of decline of CAD mortality and a cessation of reduction in CAD incidence. The epidemiology of hypercholesterolemia over this same period can now be examined with the publication of the NHANES 1999 to 2000 data and results from other surveys.[9] The results suggest little change in populationwide cholesterol levels during the past 10 years. These data also allow estimation of the OTC-eligible population of persons with hypercholesterolemia at moderate risk (10% to 20% in 10 years). The treatment gap in these subjects can then be considered, along with the populationwide benefits of lowering their LDL cholesterol levels with an OTC statin.

The availability of OTC statins remains a controversial subject. Three new surveys by the National Lipid Association (NLA) seek to define perceptions and opinions from samples of US physicians, pharmacists, and consumers. In the first of 2 articles describing the results of these surveys, Dr. Richard C. Pasternak and colleagues compare and contrast physician and consumer attitudes about cholesterol management. The level of knowledge and interest in cholesterol as a modifiable cause of CAD is high in both physicians and consumers. The barriers to lifestyle and drug strategies to reduce serum cholesterol levels described by 200 physicians include fear of side effects and reluctance to take prescription medications. The reasons identified by moderate-risk individuals for opposition to treatment with a statin include reliance on current efforts with diet and exercise and a lack of physician advice to take prescription cholesterol-lowering drugs. These surveys of knowledge and attitude form the basis for approaching physicians and patients with a new strategy, such as OTC statin availability.

A second article, by Dr. James M. McKenney and co-workers, describes the results of the NLA surveys that specifically address knowledge, attitudes, and perceptions of physicians, pharmacists, and consumers related to OTC statins. In general, physicians are more skeptical than consumers or pharmacists as to the risks and benefits of OTC statins. Concerns most frequently expressed by physicians and pharmacists include the discontinuation of prescription cholesterol-lowering drugs without discussion with a physician, drug interactions and side effects, and inability to self-manage OTC statin therapy. Pharmacists, while needing additional training in cholesterol guidelines, were accepting of a wider role in advising consumers about statin use. A large proportion of individuals reported that they would consult their physicians before initiation of OTC statins. These attitude surveys showed enthusiasm and concern about OTC statins, both of which would need to be addressed in any program that marketed them.

Consideration of OTC status for statins by the US Food and Drug Administration (FDA) has clarified the remaining issues and prompted research on consumer behaviors when OTC statins are available. The results of a recent investigation, the Consumer Use Study of OTC Mevacor (CUSTOM), are discussed by Dr. Eric P. Brass. This carefully performed study[10] describes the extent to which individuals appropriately define their risk, consult their physician, self-manage the medication, follow-up with lipid results, and comply with OTC statin instructions.

The recent withdrawal of cerivastatin because of increased cases of myopathy and rhabdomyolysis has renewed interest in monitoring blood samples for liver function tests and muscle enzymes. Dr. Allan D. Sniderman reviews updated evidence and recommendations for monitoring these tests in patients receiving statins. In the OTC situation, this would be difficult. However, the conclusion remains that there appears to be little benefit but considerable cost to monitoring liver function tests and creatinine phosphokinase. One underappreciated cost is that of follow-up evaluation of false-positive tests. OTC statins appear to carry very small risk, for which blood test monitoring is not indicated or efficient.

An intriguing new development is the approval and imminent release of OTC statins in the United Kingdom. As of July 2004, simvastatin 10 mg daily is available without prescription. Drs. David B. Nash and Stephen A. Nash discuss the reclassification of simvastatin in the United Kingdom. The situation is not entirely analogous to the United States because the United Kingdom has a "pharmacist only" (P) designation, which means that a drug can only be dispensed by and purchased from a pharmacist, providing opportunities for education about appropriate use and monitoring.

This supplement summarizes several developments that should inform any decision with regard to use of OTC statins as an acceptable strategy to enhance populationwide cholesterol reduction. In the 4 years since the initial publication,[4] the database on statin efficacy has continued to broaden while remaining impressively consistent in proof of benefits. Likewise, safety of lower-dose statins is well accepted, removing the need for laboratory monitoring or close physician supervision. Research has moved into the arena of implementation and describing consumer, physician, and pharmacist perceptions of OTC statins as an acceptable strategy. Concerns regarding how consumers would actually use OTC statins have been addressed by naturalistic studies of drug availability, with documentation of rates of appropriate and inappropriate use behaviors and their consequences. This expansion of empiric data into practical issues of OTC statin use provides the most realistic picture to date of the potential for these drugs to reinvigorate strategies for primary prevention of CAD in the United States.

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The Epidemiologic Basis for Population-wide Cholesterol Reduction in the Primary Prevention of Coronary Artery Disease

Thomas A. Pearson, MD, PhD, MPH

A number of recent epidemiologic observations support the need for new and broader strategies to reduce serum cholesterol levels on a populationwide basis. First, the limited data available suggest a halt in the declining incidence of coronary artery disease (CAD) in the United States since 1990, raising concerns about our current strategies to promote primary prevention of CAD. Data from the 1970s and 1980s support a key role for population-wide cholesterol lowering as a strategy to reduce CAD. Second, large and carefully performed surveys support no further reductions in serum cholesterol levels in the US population since 1990. Is this observation and that of stagnating declines of CAD incidence a coincidence? Interestingly, the lack of cholesterol level reduction occurred in the setting of increased use of prescription cholesterol-lowering drugs, suggesting that drug treatment of the highest-risk persons alone will not shift the population curve. Third, the treatment gap persists, with recent populationwide data suggesting that half of all people with hypercholesterolemia (≥200 mg/dL) are unaware of their condition, only half of those persons aware are treated, and only half of those treated are controlled. Finally, the moderate-risk population (10% to 20% risk of CAD over 10 years) is sizable in the ages recommended for over-the-counter statin use (≥45 years in men, ≥55 years in women). Risk reduction in this group, which contributes a significant portion of CAD cases, should be part of any program to reduce the population burden of CAD.

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The National Cholesterol Education Program (NCEP) was initiated in the late 1980s after epidemiologic and clinical trial evidence established a causal role for hypercholesterolemia in atherosclerotic cardiovascular disease. Initially, this effort consisted of 4 panels: adult treatment,[1] population,[2] laboratory methods,[3] and pediatric.[4] After these initial reports, only the Adult Treatment Panel (ATP) report has been updated to be consistent with the availability of new cholesterol treatment modalities used primarily in adults and their testing for safety and efficacy in randomized trials.[5] The Report of the Expert Panel on Population Strategies for Blood Cholesterol Reduction, released in 1990,[2] emphasized expansion of awareness of high blood cholesterol as a cause of heart disease through mass media channels, including population-wide cholesterol screening. Interventions at the population level included diet, exercise, and weight control.

The Report of the Expert Panel on Population Strategies for Blood Cholesterol Reduction[2] has not been updated in the past 15 years. However, considerable data have become available on the epidemiology of hypercholesterolemia and its consequences in the US population. Data relevant to consideration of population-wide cholesterol reduction strategies (such as over-the-counter [OTC] statin availability) include recent trends in coronary artery disease (CAD) incidence in the United States, population-wide serum cholesterol levels, and extent of detection and management of elevated cholesterol levels. Also pertinent would be the epidemiologic description of the target population for OTC statins, namely men ≥45 years of age and women ≥55 years of age at moderate risk of CAD (10% to 20% per 10 years). The purpose of this article is to review these new data as the current background and rationale for renewed, broader approaches to population-wide cholesterol reduction as a means to reduce the incidence of CAD and the subsequent burden of heart disease in the United States.

EPIDEMIOLOGIC TRENDS IN CARDIOVASCULAR DISEASE IN THE UNITED STATES SINCE 1990

The reduction of cardiovascular disease mortality in the United States since 1968 has been appropriately lauded as a major health accomplishment of the 20th century.[6] By the late 1990s, however, it was observed that cardiovascular disease rates may be subtly changing, with the reduction in CAD mortality slowing from a 2.6% per year reduction in the 1970s and 1980s to an approximate 1.5% reduction in the 1990s. Stroke mortality rates have been well documented to have had no further reductions since 1990, the first such cessation in reduction in 100 years. Risk factor levels, with the notable exception of population-wide cholesterol levels, were examined to better understand these trends.[6]

Mortality rate changes can have a number of potential explanations. After adjustments for demographic changes in a population over time, the major determinants of mortality rate changes would be

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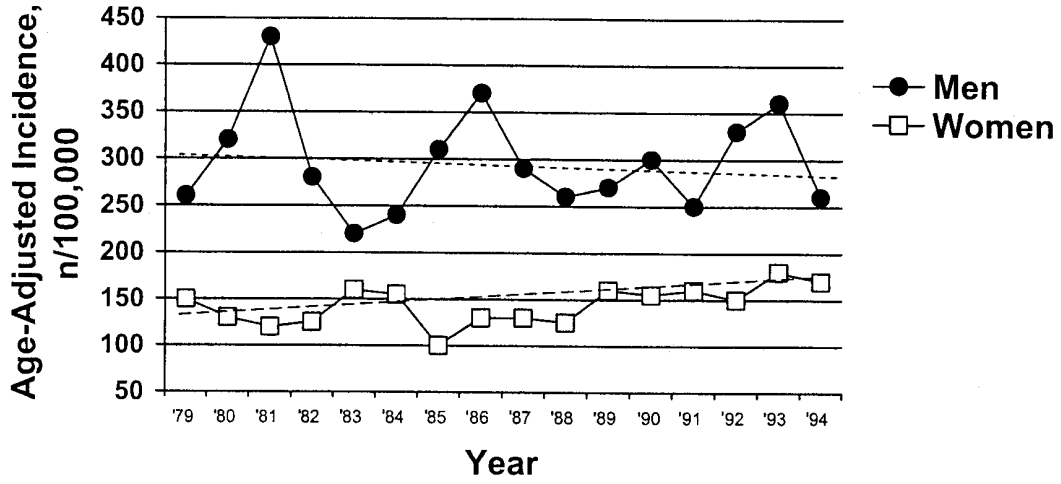

FIGURE 1. Trends in the incidence and survival of patients hospitalized with myocardial infarction in Olmsted County, Minnesota, 1979–1994. (Reprinted from *Ann Intern Med.*[8] Copyright 2002, with permission from the American College of Physicians.)

changes in incidence and/or changes in case fatality rates among those developing the disease. Population-based studies have documented progressive reductions in case fatality rates over the past 30 years, both in acute coronary syndromes and in the long-term prognosis of CAD patients.[7,8] However, relatively few community-wide studies have addressed the issue of changes in the incidence of CAD. This is a methodologic challenge for several reasons. First, cases of sudden cardiac death need to be tallied, and many of these cases do not enter the healthcare system. Second, medical databases are often unable to identify incident events and to avoid counting recurrent events as incident events. Third, there is ample opportunity for changes in diagnostic tests and case definitions to be mistaken for changes in CAD incidence. For example, the more sensitive blood tests for myocardial infarction (MI) (eg, troponins, creatine phosphokinase–MB fraction) might identify additional cases that heretofore would be classified otherwise, thereby being wrongly interpreted as an increase in incidence.

Nonetheless, at least 2 studies have examined this issue, using consistent criteria over their study durations. Goldberg et al,[7] in the Worcester (Massachusetts) Heart Study, documented sizable reductions in the incidence of acute MI between 1976 and 1988, but no further reduction in the incidence of MI from 1988 to 1996. Roger et al[8] examined the incidence of MI from 1979 to 1994 in Olmsted County, Minnesota. The incidence of MI appeared to trend downward in men and women from 1979 to 1988 (Figure 1). However, from 1988 to 1994, there appeared to be no further reduction in the incidence of MI in men and likely an increase in incidence in women. These studies emphasize the need for population surveillance to better understand and explain these trends. However, studies available in the literature support no further reduction in CAD incidence since 1990.[7,8] The decreasing case fatality rates but stable incidence rates would then translate into an increase in the prevalence of CAD cases, now estimated at 12.5 million Americans living with the diagnosis of CAD.[9] The implications of this high prevalence of CAD on disability and healthcare costs are obvious.

The role of population-wide cholesterol levels in these recent trends has not been examined. However, in the sharp declines in CAD mortality between 1970 and 1990, the reduction in mean levels of cholesterol in US adults from approximately 220 mg/dL to 205 mg/dL has been cited as a major contributor. For example, Goldman and Cook credited the decline in CAD in the 1970s primarily to reductions in population-wide cholesterol levels and cigarette smoking,[10] with a relatively smaller contribution from acute medical care.[11] These data emphasize the need for population-wide strategies to continue the downward trends in US serum cholesterol levels.

EPIDEMIOLOGY OF HYPERCHOLESTEROLEMIA IN THE UNITED STATES

Population-wide studies, such as the National Health and Nutrition Examination Surveys (NHANES), documented impressive declines in the mean serum cholesterol levels in US adults between 1970 and 1990.[12] This was largely attributed to changes in the American diet. Until recently, however, few data were available concerning cholesterol levels during the 1990s. NHANES 1999 to 2000[13] examined results from 4,148 men and women as a random sample of US adults and compared them with the results from 15,719 adults in NHANES III (performed from 1988 to 1994). The mean cholesterol levels, adjusted for age and stratified by sex, show no statistically or clinically significant change over this 10-year period (Table 1). Examination of age and sex subgroups also showed no significant changes, except in men aged ≥75 years. This lack of change in serum cholesterol levels occurred despite a modest increase in prescription cholesterol-lowering drug use (Table

TABLE 1 Age-Adjusted Mean Total Cholesterol Concentrations and Percentage of Use of Lipid-Lowering Drugs by Sex in the National Health and Nutrition Examination Survey (NHANES)[13]

	NHANES III (1988–1994)			NHANES (1999–2000)		
	N	Mean Total Cholesterol (mmol/L)	Drug Use (%)	N	Mean Total Cholesterol (mmol/L)	Drug Use (%)
Men	7,392	5.27	2.9	1,926	5.25	7.9
Women	8,327	5.34	3.3	2,189	5.28	6.8

(Adapted from *Circulation*.[13])

TABLE 2 Prevalence (%) of Serum Lipid Variables by Sex and Year in the Minnesota Heart Survey[14]

	Total Cholesterol ≥240 mg/dL or Use of Medication		Lipid-Lowering Medication Use		Total Cholesterol ≥240 mg/dL	
	Men	Women	Men	Women	Men	Women
1980–1982	22.2	20.3	1.0	0.6	22.0	20.3
1985–1987	20.5	18.1	1.4	0.5	19.8	18.1
1990–1992	19.9	17.2	2.7	2.8	18.2	16.2
1995–1997	21.2	19.3	6.0	3.9	18.0	17.5

(Adapted from *Am J Epidemiol*.[14])

TABLE 3 US Adults With Hypercholesterolemia* Who Reported Having Been Checked, Aware, Treated, and Controlled by Age Group[13]

	Age (yr)	
	45–64	≥65
Checked (%)	85.3	90.3
Aware (%)	46.5	56.0
Treated (%)	19.5	30.3
Controlled (%)†	8.2	18.1

*Total cholesterol ≥200 mg/dL.
†Total cholesterol <200 mg/dL.
(Adapted from *Circulation*.[13])

1). The NHANES databases are important because of their representativeness of the US population as a whole and the standardization of lipid values across time.

The NHANES 1999 to 2000 results[13] are corroborated by results from the Minnesota Heart Survey.[14] Four population-wide surveys from 1980 to 1997 used standardized methods to compare age-adjusted serum total and high-density lipoprotein (HDL) cholesterol levels. While HDL cholesterol levels did not change over time, total cholesterol levels decreased progressively from 1980 to 1992, from 212.2 mg/dL to 203.2 mg/dL in men and from 207.6 mg/dL to 200.6 mg/dL in women. However, from 1990 to 1992 to 1995 to 1997, no further reductions were seen (204.8 mg/dL in men, 200.5 mg/dL in women). The prevalence of prescription lipid-lowering drug use increased progressively during this period, but despite this the prevalence of persons with total cholesterol levels ≥240 mg/dL did not decrease in either men or women (Table 2).

The Minnesota Heart Survey is a rich repository of additional data that might explain trends observed in serum cholesterol levels.[14] Of interest, population-wide dietary trends in percentage of calories from saturated fat and in the Keys Score (taking into account changes in dietary saturated and polyunsaturated fats and dietary cholesterol intakes) showed reductions from 1990 to 1997 in the cholesterol-raising components of the diet and were not able to explain the lack of reduction in serum cholesterol levels. However, dietary intake of energy increased during this time period, energy expenditure in leisure exercise decreased, and body weight and body mass indices increased in both men and women. These data suggest the role of body weight in these population trends in serum cholesterol. The well-documented epidemic of obesity in the United States[15] is a plausible explanation for the disappointing trends in serum cholesterol levels observed in NHANES 1999 to 2000[13] and in the Minnesota Heart Survey.[14]

LEVELS OF DETECTION AND MANAGEMENT OF HYPERCHOLESTEROLEMIA IN THE UNITED STATES: QUANTIFYING THE TREATMENT GAP

A growing database has shown benefits from the detection and management of hypercholesterolemia in adults, and the publication and dissemination of

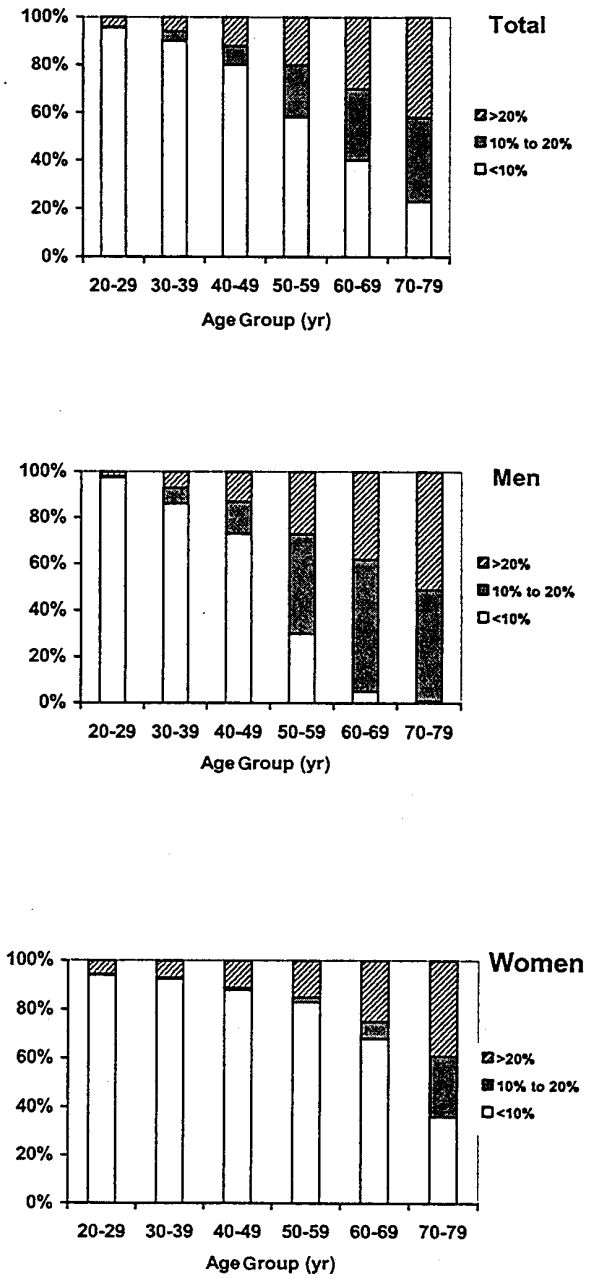

FIGURE 2. Age-specific distribution of risk for coronary artery disease (CAD) among US adults ≥20 years of age after including people with CAD or CAD equivalents in the highest risk category from the National Health and Nutrition Examination Surveys (NHANES) III Survey, 1988–1992. (Reprinted from *J Am Coll Cardiol.*[21] Copyright 2004, with permission from the American College of Cardiology Foundation.)

guidelines from the NCEP since the late 1980s have provided recommendations for screening and treatment.[1–5] Nevertheless, there remains a wide difference between the levels of detection and management recommended and those actually provided—the so-called treatment gap. It has been widely documented that US physicians are aware of these guidelines and consider hypercholesterolemia an important risk factor for CAD. Nonetheless, numerous studies have documented that physicians very frequently fail to initiate treatment[16–18] and, in those treated, fail to adjust diet and drug therapies to reach targeted cholesterol levels.[19]

Many of these studies have been performed in highly selected clinical populations (eg, academic medical centers), many of which might be expected to have a bias toward better care than the general population. NHANES 1999 to 2000[13] provides an opportunity to examine levels of screening, awareness, treatment, and control on a population-wide basis. Among persons 45 to 64 years of age or persons ≥65 years of age who were found in the survey to have an elevated serum total cholesterol level (≥200 mg/dL) or who reported using a cholesterol-lowering medication, the rates of reporting that their physicians had checked their cholesterol levels were high (Table 3). Unfortunately, considerably fewer (only 50%) were aware of having hypercholesterolemia, and fewer yet were treated. This resulted in only 8% of 45- to 64-year-old persons and 18% of persons ≥65 years old with hypercholesterolemia being identified, made aware, treated, and at target. Translated differently,[13] only 39.6% of persons with hypercholesterolemia were aware of their condition, only 14.5% reported using a cholesterol-lowering medication, and only 6.8% had a documented cholesterol level of <200 mg/dL. This suggests that the treatment gap, when viewing population-wide data, is enormous and widespread, and is certainly common in groups considered for OTC therapy.

ESTIMATION OF THE TARGET POPULATION FOR OVER-THE-COUNTER STATINS

Based on data from NHANES III (1988 to 1992),[20] prior estimations suggest that approximately 30% of US adults may be candidates for OTC statins. These estimations are based on the absence of CAD and other high-risk conditions in this population and the presence of a total cholesterol level of 200 to 239 mg/dL.[20] Using Framingham risk projections, it is estimated that this group, if untreated, would eventually contribute approximately one third of CAD cases. These data support the need for additional strategies to reduce the risk of those in the moderate-risk categories. The data also illustrate the dilemma for a large segment of the population who otherwise are less likely to be identified and treated but nonetheless eventually constitute a sizable portion of the CAD burden.

More recently, the distribution of 10-year risk of MI or CAD death using the NCEP ATP III algorithm[5] has been estimated from US adults using the NHANES III database for 1988 to 1992.[21] The data from 13,769 survey participants are representative of 157 million adults ≥20 years of age. These data identify 15.5% of US adults, or 23 million people, to be at moderate (10% to 20%) risk and an additional 2.9% (4 million) to be at high risk (>20%). However, the prevalence of moderate and high risk varies mark-

edly with age and sex (Figure 2). For example, 16% of 40- to 49-year-old men, 52% of 50- to 59-year-old men, and 81% of 60- to 69-year-old men without CAD could be at moderate risk. Fewer women would be so identified: only 8% of 60- to 69-year-olds. These data confirm that a sizable proportion (25% to 50%) of adults ≥45 years of age would be in the moderate-risk group and would likewise be expected to contribute a sizable portion of CAD cases.

CONCLUSION

Two disconcerting and likely related trends are discussed in this article, namely, the lack of decline in CAD incidence since 1990, and the lack of decline in population serum cholesterol levels over the same period. The shortcomings of current approaches are identified, both in terms of the treatment gap but also in terms of the inability of prescription drugs alone to benefit the large numbers of moderate-risk persons. Finally, recent applications of risk equations to the US population find that a large portion of adults >50 years of age have moderate risks for CAD and would be expected to contribute a substantial number of CAD cases to the overall burden of CAD. Any strategy seeking to reduce the burden of CAD on a population-wide basis would need to address this group. Availability of OTC statins is one such strategy.

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Understanding Physician and Consumer Attitudes Concerning Cholesterol Management: Results From the National Lipid Association Surveys

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Two online surveys commissioned by the National Lipid Association (NLA) were conducted to determine the current attitudes of physicians and consumers regarding cholesterol and heart disease. Physicians and consumers from preexisting independent panels were randomly invited to participate in the online surveys that were open from January 26 to 30, 2004. Both physicians (n = 200) and consumers (n = 600) agreed that high cholesterol and coronary artery disease (CAD) are significant health risks. Physicians reported the primary barriers for patients being prescribed cholesterol-lowering medication as patient fear of side effects (61%) and reluctance to take prescription medications (52%). While most physicians were aware of and felt they adhered to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, considerably fewer thought the same of other physicians. The consumer survey focused on untreated moderate-risk patients (an approximate 10% to 20% 10-year risk of myocardial infarction and cardiac death) because this group is often undertreated. Untreated moderate-risk patients reported that their physicians did not advise them to take prescription cholesterol-lowering drugs (51%) and that they were trying to control their cholesterol with diet and exercise (58%). Consumers believe they are taking an increased role in their own health management and decision making. Current attitudes of physicians and consumers are similar with regard to their recognition of the significance of cholesterol and CAD for health, but differ with regard to why patients do not take prescription medications. ©2004 by Excerpta Medica, Inc.

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Cardiovascular disease is the leading cause of death in men and women in the United States.[1] Approximately 46% of the population in the United States has a low-density lipoprotein (LDL) cholesterol level ≥130 mg/dL,[1] a known risk factor for cardiovascular disease. The safety and efficacy of statin therapy is well established, with abundant evidence showing reduction in coronary artery disease (CAD) morbidity and mortality in high-risk patients.[2–5] Lowering cholesterol has also been shown to reduce the risk of CAD in patients who are at moderate risk.[6] Given these statistics, consumer and physician awareness of the significance of high cholesterol and CAD is important for effective patient care and the prevention of CAD.

Physicians were shown to initiate both dietary and drug therapy at lower cholesterol levels in 1990 than in 1983,[7] which could reflect an increased trend in physician concern regarding high cholesterol as a serious health threat. A National Consumers League survey conducted in 2000 found that most consumers were aware that high cholesterol was a serious health threat and that reducing cholesterol could prolong life.[8] This was a continuing trend from earlier surveys that found significant increases from 1980 to 1982 to 1990 to 1992 in the percentage of adults with knowledge of their cholesterol levels and awareness of hypercholesterolemia,[9] and a rise in the percentage of patients who had their cholesterol checked from 1983 to 1990.[7] Despite this trend, Nash et al[10] recently reported that although >90% of consumers thought that it was important to have healthy cholesterol levels, only half actually knew their own level.

The overall objective of the National Lipid Association (NLA) surveys was to determine the current perceptions of physicians and consumers, particularly those at greatest risk of being undertreated by current guidelines, regarding the significance of CAD and high cholesterol, as well as the perceived barriers to treatment of each.

PATIENTS AND METHODS

Two surveys (for physicians and for consumers) commissioned by the NLA were conducted online from January 26 to 30, 2004. The surveys were drafted by Applied Research and Consulting LLC (New York, New York), an independent market research firm, and were revised by the Consumer Affairs Committee of the NLA. Because of new restrictions on telemarket-

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ers and greater Internet access by the community, Internet surveys are thought to be more representative of the general population than they were previously.[11] The objectives of the physician survey were to understand physician perceptions regarding (1) the significance of high cholesterol and CAD, (2) the need for additional efforts for CAD prevention and cholesterol management, (3) awareness and adherence to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, (4) the belief that patients can take an active role in their treatment, and (5) the barriers physicians face in treating patients at moderate risk for CAD. Physician respondents were sampled from a panel of >50,000 physicians initially recruited from medical directories and relevant medical Web sites, and who had filled out a registration form regarding details of their practice and expertise. Those physicians who were likely to treat patients with high cholesterol and who wrote ≥10 new statin prescriptions in an average month were randomly invited to participate in the online survey. Participating physicians received an incentive of $65. The sample size provided enough power to generate statistically significant comparisons when 2 subgroups were compared.

The objectives of the consumer survey were to understand the consumer perceptions regarding (1) the significance of high cholesterol and CAD, (2) the barriers patients face in preventing CAD and managing their cholesterol, and (3) the degree to which patients are willing to take an active role in their own CAD prevention and cholesterol management. Consumer respondents were drawn from a health and wellness panel of >200,000 people who were initially recruited from 400 partner Web sites, where they registered and then separately confirmed their interest and registration. Each consumer was subsequently screened regarding health problems and concerns. Those who indicated that someone in their household had high cholesterol were randomly invited to complete the online survey. To meet the inclusion criteria, consumer respondents had to be at least somewhat concerned (4 to 10 on a 10-point scale) about CAD or high cholesterol. Consumers received an incentive of $4. The sample size was larger than for the physicians because consumers are more heterogeneous in responses than physicians. The survey was also oversampled to ensure ethnic representation of respondents. The representative sample was weighted to reflect naturally occurring frequencies of population subgroups, including minorities.

Risk levels were assessed to determine whether consumers were at moderate risk and whether they were being treated or not. Moderate-risk patients are estimated to have an approximate 10-year risk of 10% to 20% for developing myocardial infarction (MI) or CAD death.[12] It has been suggested that the moderate-risk group represents the population with the most untreated individuals with hypocholesterolemia.[13] The following definition was used for untreated moderate-risk consumers: no history of prior MI or angina; no history of angioplasty, stent, or bypass surgery; no history of diabetes mellitus; total cholesterol of 200 to 240 mg/dL (and an approximate LDL cholesterol level of 130 to 170 mg/dL); plus ≥2 other risk factors, including older age (≥45 years of age for men or ≥55 for women), cigarette smoking, high-density lipoprotein (HDL) cholesterol <40 mg/dL, high blood pressure, or a family history of CAD.[12]

TABLE 1 Demographic Characteristics of the Representative Sample*

Characteristic	n (%)
Age range (yr)	
30–34	58 (9.6)
35–39	79 (13.2)
40–44	98 (16.3)
45–49	92 (15.3)
50–54	84 (14.0)
55–59	93 (15.5)
60–64	57 (9.5)
65–69	20 (3.3)
≥70	19 (3.2)
Sex	
Men	376 (62.7)
Women	224 (37.3)
Ethnicity	
White	467 (77.8)
African American	57 (9.5)
Hispanic	59 (9.8)
Asian	30 (5.0)
Other	8 (1.3)
Education level, last completed	
≤Grade 8	2 (<1)
Some high school	9 (1.5)
High school graduate	121 (20.2)
Some college	223 (37.2)
College graduate	147 (24.5)
Postgraduate work/degree	97 (16.2)
Annual household income (US dollars)	
<$25,000	100 (16.7)
$25,000–29,999	52 (8.7)
$30,000–34,999	47 (7.8)
$35,000–39,999	31 (5.2)
$40,000–49,999	76 (12.7)
$50,000–74,999	156 (26.0)
$75,000–99,999	74 (12.3)
>$100,000	63 (10.5)
Health insurance	
Yes	529 (88.2)
No	71 (11.8)
Health insurance includes prescriptions	
Yes	497 (82.8)
No	101 (16.8)

*The representative sample is weighted to reflect naturally occurring frequencies of population subgroups.

RESULTS

Physician and consumer demographics: Physicians (n = 200) who responded included 70 family practice physicians, 80 internal medicine physicians, and 50 doctors of osteopathy. The range of medical practice was 2 to 30 years beyond their residency. Consumer respondents (n = 600) were well distributed with regard to age, ethnicity, education level, and household income (Table 1). A plurality of the consumer respondents (45%) were between 45 and 54 years of age. One third of consumers (n = 200) reported cur-

rently taking prescription medication to control their cholesterol. Two thirds of consumers (n = 400) reported not currently taking prescription medication, and the majority (n = 323) were at moderate risk.

Perceptions regarding cholesterol and CAD risk: Physicians and consumers had similar attitudes toward cholesterol and CAD. The majority of physicians agreed that cholesterol (70%) and CAD (92%) are among the most important health problems today, and that an across-the-board reduction of cholesterol (approximately 25% to 35%) in the American population would greatly benefit the overall public health of our country (78%). However, only 25% of physicians felt that there was enough public attention given to the risks and significance of high cholesterol and that the link between high cholesterol and CAD is well understood by the general public (23%). Even so, few (26%) agreed that physicians do a good job of educating patients about the risks of high cholesterol. Most physicians felt that new approaches were needed to reach untreated persons (73%).

More than half (57%) of all consumer respondents believed that high cholesterol is a serious health threat; a slightly higher percentage of those who were untreated and at moderate risk for CAD felt the same (66%). The majority of consumers agreed that people should learn more about the dangers of high cholesterol (85%), and that people needed to pay more attention to their cholesterol levels and have their cholesterol tested regularly (82%). Overall, a similar percentage of consumers (80%) claimed to have had their cholesterol level checked within the last year. Fewer of the untreated, moderate-risk subgroup claimed the same (60%).

NCEP ATP III guideline awareness and adherence: Table 2 summarizes responses by physicians regarding their familiarity with and adherence to the NCEP ATP III guidelines for the treatment of patients with high cholesterol. Most physicians indicated a high degree of familiarity with and adherence to the guidelines (81%). However, a significantly lower percentage (46%) believed that physicians "in general" were familiar with and adherent to the guidelines. Physicians also thought that the guidelines have less of an impact on patients at moderate or low risk for CAD compared with the impact on patients at high risk.

When asked what they emphasize when discussing high cholesterol and CAD with a patient, most physicians indicated the patient's LDL cholesterol number (85%) and the importance of other CAD risk factors (64%). Among those issues less often emphasized were a patient's ratio of HDL to LDL or total cholesterol (37%), a numeric cholesterol treatment goal (35%), the total cholesterol number (23%), the estimated 10-year CAD risk (21%), and general (nonnumeric) risk level (12%).

Attitudes regarding the cholesterol treatment gap: Most physicians (89%) agreed that people with a moderate risk for CAD should be considered for cholesterol-lowering drug therapy, and 79% agreed that there currently are many people whose moderate risk for CAD is not being treated with cholesterol-lowering therapy.

TABLE 2 Physicians' Perceptions Regarding the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) Guidelines

Physician Response	Physicians' Responses (%)
About themselves	
Very familiar with the guidelines	81
Adherent to the guidelines	73
About other physicians in general	
Very familiar with the guidelines	46
Adherent to the guidelines	33
The guidelines have a "large impact" on patients of the following risk:	
High	73
Moderate	57
Low	25

TABLE 3 Percentage of Physicians and Untreated Moderate-Risk Consumers Who Agreed With Statements* Regarding Barriers to Use of Prescription Cholesterol-Lowering Medication

Statement	Physicians (%)	Consumers (%)
Many patients are concerned about potential side effects of prescription drugs	61	
I am afraid of the side effects of cholesterol-lowering medications		31
Many patients unable to afford prescription drugs	59	
Prescription medications cost too much		34
Many patients do not comply with long-term cholesterol-lowering treatment	58	
I often forget to take prescription medications		6
Many moderate-risk patients are reluctant to take prescription medications	52	
I don't like to take prescription medications		28
Physicians often want to enforce diet and exercise adherence before medication	28	
I am trying to control my cholesterol with diet and exercise		58

*Reworded from verbatim statements in some instances. Untreated moderate-risk consumers were asked which of the reasons presented explain why they were not currently taking prescription cholesterol-lowering medication.

Table 3 shows percentages of physicians and consumers in agreement with selected barrier statements. Physicians were asked about the potential reasons why more people who are at moderate risk for CAD are not treated with cholesterol-lowering drug therapy. A total of 50% of physicians reported that patients are not taking therapy because they are unaware of the risks of high cholesterol. Other reasons that physicians are not treating moderate-risk patients with cholesterol-lowering drug therapy included giving priority to life-

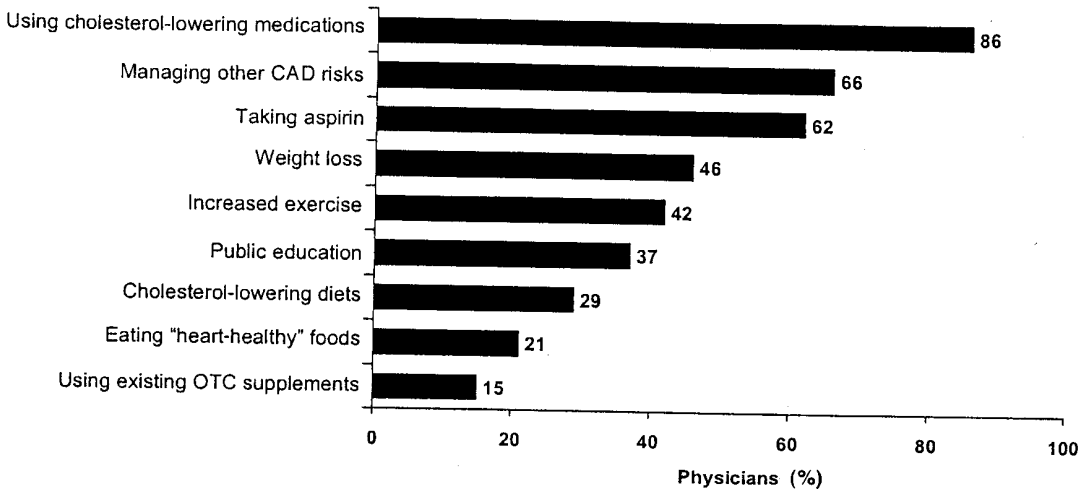

FIGURE 1. Physicians' rating of effectiveness of various approaches for treating patients who are at moderate risk for coronary artery disease (CAD). Physicians were asked to rate the effectiveness of the approaches for treating patients who are at moderate risk for CAD using a 10-point scale (from *1* = extremely ineffective to *10* = extremely effective). The percentages presented are from physicians who answered 8 to 10 on the 10-point scale. OTC = over the counter.

style modification (28%), patient preference for over-the-counter (OTC) therapy (27%), not enough time to discuss high-cholesterol issues with patients during office visits (25%), giving priority to acute, symptomatic conditions over the prevention of potential chronic disorders (22%), and constraints of modern medical practice that limit a physician's ability to identify and treat patients at risk for CAD (21%). More physicians than consumers perceived side effects, cost of prescription medication, patient nonadherence, and patient reluctance to take prescription medication as barriers to treatment.

Untreated moderate-risk consumers were asked why they were not currently taking a prescription cholesterol-lowering medication. Approximately half (51%) of untreated moderate-risk consumers reported that they did not take prescription cholesterol-lowering therapy because their physician never told them to. Other reasons cited by consumers for not taking prescription cholesterol-lowering medication included preferring to take OTC supplements or herbal products to control cholesterol (24%) and not being concerned enough about cholesterol levels to take a prescription medication (15%). Untreated moderate-risk consumers also appeared to lack physician and information resources but did not consider that a major barrier. Less than half (44%) agreed that their physician's office provided them with sufficient information to help understand how to manage cholesterol, but only 35% agreed that during an office visit, "there is often not enough time to talk about high cholesterol or heart disease" with their physician or nurse. Only 35% said they wished there were more convenient ways to obtain information about cholesterol and heart disease, and more than half (55%) said they knew where to look for information about high cholesterol and heart disease.

Perceptions regarding treatment effectiveness and patient involvement: Figure 1 illustrates physicians' ratings of the effectiveness of various therapies for people who are at moderate risk for CAD. The most effective therapies cited by physicians were cholesterol-lowering medications (86%) and managing other CAD risk factors (66%). Approximately two thirds (67%) of physicians typically recommend lifestyle changes for moderate-risk patients for ≥3 months before considering a prescription lipid-lowering therapy. Physicians (67%) also reported that they eventually treat most or all moderate-risk patients with prescription medications.

Most untreated moderate-risk consumers (77%) agreed that even high cholesterol can be lowered without medication by eating right and exercising. When asked about the actions currently taken to help maintain heart health, 28% reported regularly eating a low-fat diet (28%), and 29% reported exercising regularly. Surprisingly, only 28% of untreated moderate-risk consumers agreed that it was difficult to control cholesterol through diet and exercise.

The majority of untreated moderate-risk respondents said that it was important to actively participate in their own health management (86%), that it was important to work with their physician to manage serious health conditions (81%), and that they are willing and able to participate in their own health management (80%). In fact, only 1% disagreed with the latter. A significantly higher ($p < 0.05$) percentage of treated respondents agreed that it was important to actively participate in their own health management (92%), and to work with their physician to manage serious health conditions (90%). Additionally, 54% of untreated moderate-risk consumers reported making more health decisions now than they did 5 years ago. Conversely, 30% of physicians agreed that patients

TABLE 4 Actions Currently Taken on a Regular Basis by Treated and Untreated Moderate-Risk Consumers to Maintain Their Heart Health*

	UMR (n = 323), %	Treated (n = 200), %
Demographics		
Age ≥50 yr	55	62
Age <50 yr	45	38
Men	32	45
Women	68	56
Income < US $50,000/yr	53	47
Income ≥ US $50,000/yr	47	53
Action regularly taken		
Refrain from smoking	53	70
Visit the doctor	44	81
Eat heart-healthy foods†	41	48
Try to lose weight	38	48
Get your cholesterol levels tested	33	86§
Eat a low-sodium diet	31	43
Use OTC supplements‡	29	39
Exercise	29	28
Eat a low-fat diet	28	41
Take aspirin	25	52
Eat a low-carbohydrate diet	13	21

OTC = over the counter; UMR = untreated moderate-risk.

*Consumers were asked to consider the listed actions they currently take to maintain their heart health, then indicate whether they do the action regularly, often, rarely, or never.

†Heart-healthy foods include oatmeal, nuts, Cheerios cereal (General Mills, LLC, Minneapolis, MN), cholesterol-lowering margarines, or other products.

‡OTC supplements include garlic, fish oil, red rice yeast, niacin, or other products.

§Significant difference ($p < 0.05$) between UMR and treated respondents.

TABLE 5 Physicians' Treatment Approach to the Moderate-Risk Patient

Characteristic	Physician Responses (%)
Patients prescribed lifestyle modification	
All	0
Most	39
Some	43
Few	15
None	3
Time to continue lifestyle modification before considering medication	
<1 mo	5
1–2 mo	30
3–6 mo	49
7–12 mo	12
>12 mo	6
Patients ultimately prescribed cholesterol-lowering therapy	
All	8
Most	59
Some	32
Few	2
None	0
LDL treatment goal set for these patients (mg/dL)	
<100	24
<130	72
<160	4
Do not typically focus on treatment to LDL goal	1

are unwilling or unable to participate in their own health management.

Table 4 compares practices of treated moderate-risk patients with those of untreated moderate-risk individuals. Having been treated for high cholesterol correlates with higher levels of self-care. The largest differences between treated and untreated moderate-risk groups were refraining from smoking, visiting their physician, having cholesterol checked, and taking aspirin. All responses, except for exercising and eating foods that can help reduce heart disease, were significantly different between the groups ($p < 0.05$).

Treated and untreated moderate-risk consumers also had different knowledge of their total cholesterol levels (Figure 2). Significantly more ($p < 0.05$) treated patients (42%) reported knowing their exact total cholesterol levels than untreated moderate-risk individuals (26%).

Physician response to the treatment of moderate-risk patients: In an attempt to understand how physicians approach the treatment of moderate-risk patients, a patient scenario was created and questions were asked of the physicians regarding the scenario. The patient scenario was the following: no history or other evidence of CAD, peripheral vascular disease, stroke, or diabetes; the presence of ≥2 CAD risk factors; and an approximate 10% to 20% chance of having an MI or CAD event in the next 10 years. The physician responses to the various questions posed are shown in Table 5. Although 67% of physicians would continue lifestyle modification for ≥3 months before starting a medication, a similar 67% of physicians believe that most or all such patients would ultimately be prescribed a cholesterol-lowering drug.

DISCUSSION

In this survey carried out by the NLA, current attitudes of physicians and consumers were in agreement regarding the significance of high cholesterol and CAD as serious health problems today. These consumer opinions are consistent with the 2000 National Consumers League survey, in which 89% of consumers believed that high cholesterol was a serious health threat and 92% thought that by lowering cholesterol people can prolong life.[8] Pieper et al[9] reported that knowledge of cholesterol levels significantly ($p < 0.001$) increased from 15% (1980 to 1982) to 55% (1990 to 1992) in women and from 19% to 47% for men over the same period. From 1980 to 1982 to 1990 to 1992, awareness of hypercholesterolemia more than doubled in women (from 17% to 60%) and increased from 25% to 55% in men ($p < 0.001$).

A more recent survey indicated that many consumers (91.2%) stated it was personally important to them to have a healthy cholesterol level.[10] However, 51% did not know their own level, and only 40.2% were aware of the national guidelines for cholesterol management. In the NLA survey, most consumers (66%) did not know their exact total cholesterol level, although significantly more of those being treated knew

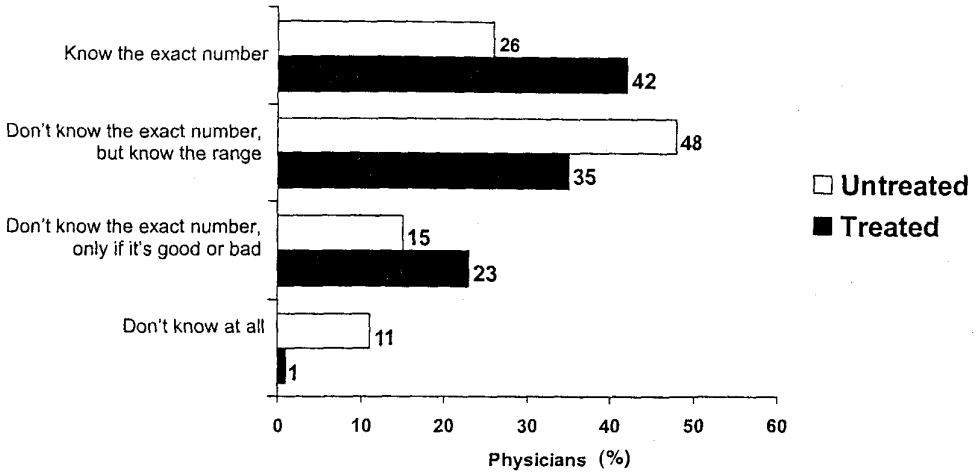

FIGURE 2. Self-reported knowledge of total cholesterol among treated and untreated moderate-risk survey respondents. Consumers were asked which of the following best described their knowledge of their total cholesterol level: "I know the exact number"; "I don't know the exact number, but know the range"; "I don't know the exact number, but I know whether it is good or bad"; "I don't know at all." *p <0.05 for between-group differences.

their total cholesterol level than untreated moderate-risk patients.

Previous surveys have shown that an increase in patient knowledge of cholesterol and hypercholesterolemia awareness corresponded with the educational initiatives of the NCEP.[9] They also found an increase in both men (7% to 13%) and women (9% to 14%) for the prevalence of current pharmacologic treatment for patients reporting physician-diagnosed hypercholesterolemia.[9] Physicians surveyed here reported that they were personally familiar with and adherent to the NCEP ATP III guidelines. This response was similar to the 90% of physicians (N = 1,600 surveyed) who reported being aware of and using the NCEP ATP guidelines in 1990. The survey reported by Schucker et al[7] also illustrated the trend of initiating diet or drug therapy in patients with lower cholesterol levels in 1990 compared with 1983.

Physicians and consumers differed regarding barriers for patients taking cholesterol-lowering medication. The fact that physicians and consumers report different reasons for nontreatment with prescription cholesterol-lowering therapy suggests that better communication regarding cholesterol management is needed between physicians and patients. Physicians reported that patients are not taking prescription cholesterol-lowering therapy because patients are unaware of the risks of high cholesterol. However, this response is inconsistent with consumer responses.

Awareness of high cholesterol as a significant health risk may be reflected in an increase in patient self-care regarding cholesterol management. The NLA survey shows that most consumers thought it was important to work with their physicians to manage important health issues, including having cholesterol levels checked. In their surveys of >4,000 adults in 1983, 1986, and 1990, Schucker et al[7] found an increase in the percentage of patients who had their cholesterol levels checked from 1983 to 1990. In 1983, 35% of patients had their cholesterol levels checked, whereas 65% had their cholesterol levels checked in 1990.[7] In addition, an increase from 1983 to 1990 was reported by consumers for physician diagnosis of high cholesterol (from 7% to 16%), self-initiated diet efforts (from 1% to 15%), and reported prescription of a cholesterol-lowering diet (from 3% to 9%), which may reflect an increase in physician visits, an important aspect of self-care.

An increasing trend in consumers taking control of their own health care is that more than half of the consumers in the NLA survey were found to make more health decisions now than in the past 5 years. This response is consistent with that reported in the 2000 National Consumers League survey,[8] which found that 58% of consumers were making more of their own healthcare decisions now compared with 5 years earlier. Clearly, physicians can help facilitate patient involvement in their own care through better patient–physician communication. Epstein et al[14] recently presented recommendations for incorporating evidence into clinical conversations to facilitate patient involvement in their own health management: (1) understand the patient's and family members' expectations, (2) build a partnership with the patient through empathy, which builds trust and facilitates transfer of important information, (3) present evidence to the patient, including a balanced discussion of uncertainties, (4) present their recommendations, but only after the clinician has integrated clinical evidence with patient values, and (5) have the physician check for patient understanding and agreement, which may include having the patient summarize what he or she understands from their discussion. Our NLA survey suggests that consumers are likely to be primed for these levels of improvement in communication.

This study is limited in that the results may not be applicable to all physicians or to the general population because of the physician and consumer selection

criteria. The physician sample was limited to those who were likely to treat patients with high cholesterol and who wrote ≥10 new statin prescriptions per month. The consumer sample was also limited in that consumers had someone in their household with high cholesterol and were at least somewhat concerned about CAD or high cholesterol. Although the effect of this selection bias on physician and consumer responses is unclear, the survey results presented here are more likely to represent the attitudes of physicians and consumers with greater than average awareness and interest in the treatment of high cholesterol.

CONCLUSION

This NLA survey found that physicians and consumers agreed that high cholesterol and CAD are important health risks. The current attitudes of both physicians and consumers show a continuation of the trend of increased awareness, among both groups, of the significance of high cholesterol and CAD for their health, and the need for better physician–patient communication concerning treatment options for health-conscious moderate-risk patients.

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The National Lipid Association Surveys of Consumers, Physicians, and Pharmacists Regarding an Over-the-Counter Statin in the United States: Is This a Good Idea?

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Surveys commissioned by the National Lipid Association (NLA) were conducted to determine the current attitudes and perceptions of physicians, consumers, and pharmacists regarding the impact of an over-the-counter (OTC) statin. Individuals from preexisting independent databases were randomly invited to participate in the online surveys that were open from January 26 to 30, 2004 for physicians and consumers and from March 1 to 12, 2004 for pharmacists. The results of these surveys indicate that consumers and pharmacists are more positive regarding the idea of an OTC statin, whereas physicians are more guarded. Concerns of both physicians and pharmacists included the discontinuation by patients of their prescription cholesterol-lowering therapy without consulting their physician, safety issues such as potential drug interactions and side effects, and patient ability to self-manage OTC statins. Consumers interested in purchasing an OTC statin reported that they would consult their physician before doing so, and pharmacists were interested in supporting consumers who use OTC statins. Although such support would require further training and time, pharmacists believed that they could facilitate consumer self-care programs and follow-up with physicians. ©2004 by Excerpta Medica, Inc.

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Moving statin therapy from prescription-only to over-the-counter (OTC) status would mark a major turning point for this drug class and for OTC therapy in general. OTC therapies have been approved by the US Food and Drug Administration (FDA) for the symptomatic relief of common conditions, usually of short duration. However, no OTC therapies have been approved by the FDA for managing lipid disorders. Certain foods have received FDA approval to claim heart disease prevention qualities via the lowering of cholesterol, such as whole oat foods (eg, oat bran, oatmeal, whole oat flour) and those containing plant sterols or stanol esters (spreads, salad dressings, snack bars, and dietary supplements in softgel form).[1,2] Numerous dietary supplements (eg, garlic, flaxseed, niacin), which are not approved by the FDA for heart disease prevention or lipid management, also claim these benefits. For the first time, the availability of an OTC statin would provide the consumer with an FDA-approved OTC therapy for prevention of future coronary events. FDA approval of an OTC statin would provide assurances that the product meets certain quality standards through good manufacturing practices and that associated adverse effects would be documented and addressed through an ongoing drug surveillance program.

In spite of these and other advantages, many questions must be resolved before an OTC statin is made available, including what consumers and healthcare professionals think of this option and whether consumers can successfully self-manage this therapy. Can consumers decide whether an OTC statin is their best option (ie, instead of more aggressive medical management), confirm that it is not contraindicated, avoid interacting drugs, monitor their cholesterol levels to ensure adequate control, and identify and manage associated side effects? Healthcare professionals and regulatory authorities will need to determine whether OTC statins are safe for general consumption, which patient group is best suited to receive this treatment, how consumers can be properly supported to carry out their treatment successfully, how patients will receive more aggressive physician-directed care when needed, and whether OTC statin therapy can importantly contribute to an overall reduction in coronary artery disease (CAD), which is the leading cause of mortality in the United States.

Another important issue in the OTC discussion is the role of pharmacists, who spend part of each day answering questions and providing advice to consumers about OTC therapy. In an ideal situation, an OTC statin would be sold only where pharmacists would help consumers with their decision to purchase this therapy and assist in monitoring its effects. Whether pharmacists have the time, interest, and training for this task remains to be seen.

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TABLE 1 Description of Over-the-Counter (OTC) Statin to Consumers, Physicians, and Pharmacists*

Consumers	Physicians and Pharmacists
The FDA is currently evaluating a new nonprescription, over-the-counter medication that can help you have a healthier heart by controlling your cholesterol. It has been taken by millions of people for the past 15 years as a prescription medication and, if approved, would be the first product of its kind to be available in nonprescription form. It is a small pill taken once a day that reduces the risk of heart attack and stroke by up to 37% by lowering your "bad cholesterol" and raising your heart-protective "good cholesterol." This product is available in a low dose that is appropriate only for people with "borderline" cholesterol levels (total cholesterol 200–240 mg/dL) who are at risk for heart disease but have *not* had a heart attack, stroke, heart disease, or diabetes, or are *not* currently taking a prescription cholesterol-lowering medication.	The FDA is evaluating the appropriateness of granting OTC availability for several low-dose statin products (such as 20 mg lovastatin or 20 mg pravastatin) to be used for primary prevention by consumers who are not currently taking a cholesterol-lowering medication and who have moderate risk for CAD: • Have an LDL cholesterol level of 130–170 mg/dL (approximate total cholesterol level of 200–240 mg/dL) • Are men aged ≥45 years, or women aged ≥55 years. • Have ≥1 additional risk factor (cigarette smoking, HDL cholesterol level of <40 mg/dL, family history of CAD, high blood pressure) • Have not had a heart attack, stroke, angina, or diabetes The OTC dose would be expected to allow a substantial portion of the target population (described above) to attain the NCEP ATP III goal of having an LDL-cholesterol level of 130 mg/dL. The OTC dose has also been shown in numerous landmark studies to have side effects equivalent to placebo (including any muscle or liver concerns).

CAD = coronary artery disease; FDA = US Food and Drug Administration; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

*Reworded from verbatim statements in some instances. Untreated moderate-risk consumers were asked which of the reasons provided, explained why they were not currently taking prescription cholesterol-lowering medication.

Given these questions, the National Lipid Association (NLA) conducted surveys of consumers, physicians, and pharmacists to record and analyze their attitudes and perceptions about the possibility of an OTC statin option. This article reviews the findings.

PATIENTS AND METHODS

Detailed objectives, methodology, and recruitment methods for physicians and patients are detailed by Pasternak et al elsewhere in this supplement.[3] Three surveys commissioned by the NLA were conducted online: the surveys were open from January 26 to 30, 2004, for physicians and consumers and from March 1 to 12, 2004, for licensed pharmacists. Physicians or pharmacists who were consultants or clinical investigators for pharmaceutical companies were excluded.

Physician respondents were sampled from a panel of >50,000 physicians. Those likely to treat patients with high cholesterol were randomly invited to participate in the online survey. Physicians received an incentive of $65. An estimated sample size of 200 physicians provides enough power to generate statistically significant comparisons at a reasonable confidence level when 2 subgroups are compared.

Consumer respondents were drawn from a health and wellness panel of >200,000 consumers. Each individual was subsequently screened regarding his or her health problems and concerns. Those who indicated that someone in their household had high cholesterol were randomly invited to complete the online survey. Consumers received an incentive of $4. The survey was also oversampled to include ethnic and racial representation among respondents.

Pharmacist respondents were drawn from a database of 2,552 licensed pharmacists provided by the American Pharmacy Association. All respondents were required to have practiced for no more than 40 years since their licensure. Pharmacists received a gift certificate worth $50 in American Pharmacy Association merchandise (eg, professional texts) as an incentive.

The online questionnaires inquired about current attitudes regarding the possible availability of an OTC statin. Participants were presented with a description of an OTC statin (Table 1) followed by questions regarding their attitudes and perceptions about this option. Responses of 8 to 10 on the respective 10-point scale for each question (where 0 indicated no agreement and 10 indicated full agreement) are reported here. Differences between select subgroups were examined by independent t test (for means) and z test (for percentages) for significance at a 95% confidence interval. In this survey, high-risk consumers included those who indicated that they had experienced a prior heart attack; had angina, stroke, or diabetes mellitus; or had undergone angioplasty or bypass surgery. Moderate-risk consumers included those who claimed to have a total cholesterol level between 200 and 240 mg/dL and ≥2 major CAD risk factors (but no CAD or CAD risk equivalent) as identified by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).[4]

RESULTS

Physician, consumer, and pharmacist demographics: The demographic details of the consumers (n = 600) and physicians (n = 200) are reported elsewhere.[3]

TABLE 2 Consumer, Physician, and Pharmacist Acceptance of an Over-the-Counter (OTC) Statin Option*

	Consumers (%)	Physicians (%)	Pharmacists (%)
Interested in learning more about an OTC statin	72	51	86
Interested in purchasing (consumers), or supporting a patient interested in taking (healthcare professionals), an OTC statin	53	45	68

*Data represent selection of 8 to 10 on a 10-point scale.

TABLE 3 Concerns Cited by Physicians and Pharmacists About Over-the-Counter (OTC) Statins*

Concern	Physicians (%)	Pharmacists (%)
Patients discontinuing prescription lipid-lowering therapy	75	79
Potential drug interactions and side effects with OTC statins	73	79
Patient ability to self-manage OTC statin usage (lipid testing, compliance)	72	78
Patients further distancing themselves from their physicians or healthcare system	66	56
Effectiveness of low-dose statins	47	49
Increased out-of-pocket costs	38	52

*Data represent selection of 8 to 10 on a 10-point scale.

Overall, consumer respondents (n = 600) were well distributed with regard to age, ethnicity, education level, and household income. Physicians (n = 200) who responded included 70 family practice physicians, 80 internal medicine physicians, and 50 doctors of osteopathy. All physician respondents reported practicing medicine for 2 to 30 years since their residency and writing 10 to 50 new statin prescriptions in an average month. Pharmacist respondents (n = 273) included 104 independent pharmacists and 169 chain pharmacists (99 drugstore, 45 supermarket, and 25 mass market). Representation of pharmacists regarding the number of years in practice was well distributed as follows: <5 years (21%), 6 to 10 years (16%), 11 to 20 years (17%), 21 to 30 years (30%), and 31 to 40 years (16%). Pharmacists filled an average of 130 new prescriptions for statin therapy in an average month.

Consumer, physician, and pharmacist acceptance of OTC statins: We asked consumers, physicians, and pharmacists if they would be interested in learning more about OTC statins if the FDA approved one. Most consumers (72%) were highly interested (scores of 8 to 10 on a 10-point scale) in learning more about OTC statins, whereas a relatively higher percentage of pharmacists but relatively lower percentage of physicians were highly interested in learning more (Table 2). Consumers currently on cholesterol-lowering therapy showed no greater interest in learning more than those who had never been treated (70% vs 74%, respectively). Significantly more consumers ($p < 0.05$) in the moderate-risk category (81%), the patient group potentially best suited for OTC statin therapy, were highly interested in learning more than high-risk (CAD and CAD risk equivalent) consumers (62%).

Similar results were obtained when consumers were asked how likely they would be to purchase and take an OTC statin and when healthcare professionals were asked how supportive they would be of consumers who chose to take these medications. A little more than half of all consumers queried (53%) indicated they would be highly likely (scores of 8 to 10 on a 10-point scale) to purchase and take an OTC statin. Fewer physicians were supportive of patients who wished to pursue this option, whereas more pharmacists than consumers and physicians were supportive (Table 2). About the same proportion of consumers currently on lipid-lowering treatment compared with those never on treatment (50% vs 56%) were interested in purchasing OTC statins. However, significantly more ($p < 0.05$) moderate-risk than high-risk consumers (64% vs 44%) indicated a high likelihood of purchasing and taking OTC statins.

A strong majority of consumers (83%) indicated that they would talk with their physician or other healthcare professional before purchasing an OTC statin; 5% indicated they would purchase the product and then speak with a healthcare professional; 10% said they would purchase the product without speaking with a healthcare professional; and 2% did not know what they would do. Consumers who were currently taking lipid-modifying therapy were much more likely to speak with a healthcare professional before their purchase (91%) than those who were never on treat-

TABLE 4 Physician and Pharmacist Perceptions of the Potential Benefit of Over-the-Counter Statins*

Potential Benefit	Physicians (%)	Pharmacists (%)
Increased the awareness of high cholesterol and CAD	31	49
Increased level of treatment of patients with borderline cholesterol levels and moderate CAD risk	29	40
Increased patient participation in self-managing cardiovascular health	27	34

CAD = coronary artery disease.
*Data represent selection of 8 to 10 on a 10-point scale.

TABLE 5 Percentage of Pharmacists Interested in Providing the Specified Support of Over-the-Counter (OTC) Statin Therapy*

Support	Pharmacists (%)
Answering questions about an OTC statin	85
Providing consumers with information resources about CAD prevention and cholesterol management	83
Giving advice about OTC statins	79
Assisting patients in determining the appropriateness of OTC statins for them	75
Referring patients interested in OTC statin therapy to their physician or nurse practitioner for risk-factor management	70
Monitoring patient's response to an OTC statin for adverse effects and drug interactions	68
Monitoring patient's response to an OTC statin with cholesterol testing	62
Monitoring patient adherence to an OTC statin regimen	60

CAD = coronary artery disease.
*Data represent selection of 8 to 10 on a 10-point scale.

ment (78%) ($p < 0.05$). After purchasing an OTC statin, most consumers (83%) indicated a high likelihood that they would continue to talk with their physician or other healthcare professional. High-risk consumers were more likely to do this than moderate-risk consumers (93% vs 81%; $p < 0.05$), as were currently treated compared with never-treated consumers (91% vs 75%; $p < 0.05$).

Consumers indicated that their most useful source of healthcare information was their physician (89%), with the next most common sources being the Internet (65%), a pharmacist (37%), magazines and newspapers (33%), and a nurse or nurse practitioner (32%). A total of 80% of consumers indicated that they had obtained a cholesterol blood test in the past year. However, only 34% claimed that they knew their exact total cholesterol level, and even fewer (21%) claimed they knew their exact low-density lipoprotein (LDL) cholesterol level (excluding 3% who had never heard of LDL cholesterol).

Physician and pharmacist concerns regarding perceived benefits of OTC statins: Physicians and pharmacists were congruent in their concerns about an OTC statin option (Table 3). Both groups were highly concerned about discontinuation by patients of prescription lipid-lowering therapy without talking to their physicians, safety issues such as potential drug interactions and side effects, and patient ability to successfully self-manage their use of OTC statins, especially obtaining and interpreting cholesterol testing and maintaining long-term adherence to treatment. There was less concern about the adequacy of low-dose statins to provide benefit and the additional healthcare costs that would be introduced by OTC statins.

Regarding the potential benefits of an OTC statin, fewer than half of the physicians and pharmacists thought it highly likely (scores of 8 to 10 on a 10-point scale) that the availability of an OTC statin would increase the awareness of high cholesterol levels or CAD among consumers, increase levels of treatment of patients with borderline cholesterol levels and moderate CAD risk, or increase patient participation in managing cardiovascular health (Table 4). However, physicians (68%) and pharmacists (82%) rated OTC statins as "more effective" in lowering cholesterol levels than currently available nonprescription cholesterol-lowering dietary and herbal supplements.

Pharmacist interest in an increased role in management of OTC statins: The majority of pharmacist respondents (64%) were positive about providing pharmacy services to patients in support of OTC statin treatments. The highest percentages of pharmacists were interested in providing services traditionally given in the course of their day: answering patient questions, giving advice about OTC therapy, and helping patients determine whether OTC therapy is appro-

priate for them (Table 5). However, most pharmacists were also interested in referring consumers to physicians for the management of risk factors and in monitoring consumers taking OTC statin therapy. To effectively advise patients about OTC statins, 68% of pharmacists agreed that they would need to learn more about the NCEP ATP III treatment guidelines. Only 37% of pharmacists were concerned about the extra demands these services would place on their time. However, 63% were concerned about their ability to obtain sufficient knowledge regarding the patient's health.

DISCUSSION

The results of the NLA surveys indicate that consumers and pharmacists are more positive than physicians about an OTC statin option. However, physicians as well as pharmacists have concerns that consumers will discontinue their prescription therapy, experience side effects and drug interactions, and be unable to self-manage use of OTC statins successfully. Consumers, especially those who have never received treatment or diagnosis for high CAD risk, report that they will continue to consult their physician while taking an OTC statin. Pharmacists are interested in providing services to help consumers successfully use an OTC statin. Although this would require further training and time, their role may facilitate consumer self-care programs and follow-up with a physician.

This NLA consumer survey indicates that respondents are generally enthusiastic about having an OTC statin option. The majority of potential consumers are moderate-risk individuals, the consumer group best suited for OTC statin therapy. However, the survey also indicates that some currently treated and high-risk patients would also purchase and take this therapy, which raises obvious concerns. It is hoped that these individuals would be discouraged from doing so after reading the product labeling; calling a toll-free help line; and/or consulting their physician, pharmacist, or other healthcare professional. The survey indicates that 83% of consumers would consult their physician before purchasing the product.

Physicians are cautious, even reticent, about an OTC statin option, as indicated by the results of their survey. Only about half wanted to learn more about this option, and fewer would support a consumer who is interested in pursuing it. Physician reluctance is likely due to the perception that OTC statin therapy could conflict with the patient's medical care. Physicians may also recognize the complexity of the decisions that need to be made to initiate and successfully carry out OTC statin therapy. In fact, both physicians and pharmacists were concerned that OTC statin therapy would divert patients from more effective prescription therapy; they also expressed concern about side effects, drug interactions, and the patient's ability to self-manage OTC statin therapy.

Reservations about the safety of OTC statin therapy may be exaggerated. The NCEP ATP III and recent statements on statin safety by the American Heart Association, the American College of Cardiology, and the National Heart, Lung, and Blood Institute indicate that these drugs are very safe[4,5]—as safe as, and perhaps safer than, aspirin therapy used for stroke prophylaxis. The potential for myositis and rhabdomyolysis with an OTC low-dose statin is likely to be small; the potential for serious hepatic dysfunction is even smaller. However, if these adverse effects occur even rarely, the question arises as to how patients will know that a potentially serious adverse effect is occurring, and how they will obtain help to deal with it. An interaction with a coadministered drug that causes a rise in statin blood levels may be a minor concern with low-dose statin therapy, but even a rare adverse occurrence needs to be anticipated. Thus, the question remains as to how patients will know which drugs to avoid and what symptoms should prompt professional consultation.

Despite the concerns of physicians and pharmacists, the NLA consumer survey suggests that consumers may be successful in using an OTC statin. Most respondents indicated that they would consult their physician or another healthcare professional before purchasing such a drug, and that they would continue to do so while taking the statin. Additionally, physicians were cited by the consumers as the most common source of health information, with the Internet and pharmacists the next most popular responses respectively. A prior survey conducted by the National Consumers League reported that consumers were somewhat to very likely to consult their physician before starting OTC statin therapy (86%) and would only use the product if their physician approved (87%) or if they understood the labeling information (78%).[6] This survey also found that the majority of consumers would continue to talk to their physician (91%) and ask their pharmacist questions (83%) while taking the product.

An important issue is whether consumers will adhere to self-directed OTC statin therapy long enough to achieve benefit. Nothing in the NLA survey addresses this question. However, the article by Brass[8] elsewhere in this supplement, as well as an earlier study[7] showing that 57% of self-treated patients completed 12 months of OTC statin therapy,[7,8] suggest that adherence to therapy is not substantially different from what has been reported with prescription cholesterol-lowering therapy.[9]

Another important question for successful OTC therapy is whether consumers can obtain their cholesterol profile and determine whether they have achieved their LDL-cholesterol treatment goal. The NLA survey indicated that 80% of consumers had obtained their cholesterol levels in the past year, suggesting that patients could obtain these tests. However, approximately two thirds of consumers did not know their exact total cholesterol level, and three quarters did not know their LDL cholesterol numbers. Knowledge and interpretation of this information are essential for self-management of OTC statin therapy as well as for determining adequacy of treatment. In prior surveys of >4,000 adults in 1983, 1986, and 1990, Schucker et al[10] found a rise in the percentage of

patients who had their cholesterol checked (from 35% to 65%), possibly indicating an increased trend toward patient self-care.

The support of pharmacists may turn out to be key to successful use of OTC statin therapy. If pharmacists are to assist patients with OTC statin therapy, the NLA survey results are reassuring. Most pharmacists were interested in helping consumers make the right choice and in giving them information and advice about OTC statins. Also, most pharmacists were interested in referring patients to physicians for the management of risk factors. This could be an important way to separate patients requiring more aggressive, physician-directed lipid management from those deemed most suitable for OTC therapy. A study conducted by Sclar et al[11] has indicated that pharmacy consultation can significantly influence consumer purchase of OTC products.

Although pharmacist-respondents in the NLA survey indicated interest in helping consumers learn about OTC statin therapy, arrange for follow-up lipid testing, and provide monitoring and advice, it must be noted that these services are currently not routinely available from pharmacists. Moreover, to our knowledge, no plan to provide them with training specific to management of OTC statin option been proposed. In the United Kingdom, where the OTC statin is a third class of drugs (one that is sold only by pharmacists), the pharmacist's participation is assured. However, the United States does not have a third drug class, and thus the interaction between the consumer and pharmacist cannot be assured or required. Additionally, US pharmacists will have to be trained and find the time to provide these services. The NLA survey indicates that most pharmacists want additional training if they are to provide these services, and few were concerned with the time demand these services would impose. US pharmacists undergo a rigorous education before licensure, so updating their knowledge and skills to support OTC statin therapy should not pose a major problem. The more important question remains as to how consumers will avail themselves of such services.

CONCLUSION

The NLA surveys indicate that consumers are positive about the availability of an OTC statin option. Although pharmacists were more positive than physicians, they have similar concerns about patient behavior and safety. The surveys indicate that consumers will seek advice and guidance from healthcare professionals to take OTC statin therapy, but the big question is how they will get it. The NLA believes that the question regarding an OTC statin option is less about the benefit of treatment, because effective CAD risk reduction has already been documented in several large randomized clinical trials, or about safety, because OTC statin therapies have proved safe in many long-term clinical trials involving thousands of person-years.[12] Rather, the key question is how the consumer will be supported to carry out safe, wise, and effective self-care to prevent CAD events. This is the topic that will require ongoing professional and consumer discussion and debate if and when an OTC statin option is approved for the US market.

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Consumer Behavior in the Setting of Over-the-Counter Statin Availability: Lessons from the Consumer Use Study of OTC Mevacor

Eric P. Brass, MD, PhD

Despite the proven benefits of statins, large numbers of patients meeting guideline criteria for therapy are not receiving these drugs. It has been suggested that over-the-counter (OTC) availability of statins would allow more consumers to use statins and achieve cardiovascular risk reduction. However, concerns have been raised as to the consumers' ability to self-manage hyperlipidemia and use statins safely. The Consumer Use Study of OTC Mevacor (CUSTOM) was designed to define consumer behaviors in the setting of OTC statin availability. The study was conducted in a simulated OTC setting and allowed consumers to purchase once-daily lovastatin 20 mg. The CUSTOM dataset includes >3,300 consumers who evaluated OTC lovastatin for potential purchase at study sites and follow-up information on purchasers for up to 6 months of self-managed therapy. These data have been analyzed to address consumers' knowledge of their cholesterol concentrations as well as their ability to make OTC use decisions based on their cardiovascular risk, avoid drug–drug interactions, self-manage their cholesterol treatment after deciding to use the OTC product, and maintain interactions with physicians while using lovastatin OTC. The results showed that most study participants appropriately self-selected OTC statin therapy and managed their treatment. Use of OTC statins by consumers needing more intensive statin therapy or facing the risk of potential drug–drug interactions remains an area of concern but occurred infrequently in CUSTOM. These data are important for making an informed risk-benefit decision concerning OTC statin availability. ©2004 by Excerpta Medica, Inc.

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The efficacy of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) in reducing cardiovascular events and mortality has been established in multiple populations encompassing both primary and secondary prevention. This clinical trial experience has been integrated in the recommendations of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).[1] Among these recommendations is the initiation of hypolipidemic therapy for patients with ≥2 cardiovascular risk factors and a Framingham risk score yielding an estimated 10-year risk for coronary events of <20%, with a goal of achieving a low-density lipoprotein (LDL) cholesterol of <130 mg/dL.

Despite the unambiguous clinical trial data and multiple consensus panels and recommendations, studies have shown that only a small percentage of patients meeting criteria for treatment with statins are receiving this therapy.[2–4] Although various strategies have been used to increase statin therapy in target populations, the number of eligible patients taking statins has remained disappointing. This low utilization translates to increased cardiovascular morbidity and mortality, as well as increased healthcare costs.

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It has been suggested that the over-the-counter (OTC) availability of statins would increase the prevalence of statin therapy in at-risk populations.[5] OTC availability would remove some of the barriers to statin access, including the need to obtain prescriptions from a physician, and might decrease patient costs, depending on an individual patient's health insurance status. OTC availability might be particularly rational for use as primary prevention in patients with limited comorbidities because those patients are less likely to be under the intensive care of a healthcare professional.

The OTC availability of a drug that has previously been available only by prescription raises a number of issues for patients, healthcare providers, and the integrated healthcare delivery system.[6] The use of a prescription drug requires a healthcare professional to assess the patient and determine that the patient has the indication for which the drug is intended, confirm that the patient has no contraindications for use of the drug (comorbidities or potential for drug interactions), monitor the patient for drug efficacy and potential adverse events, and educate the patient (by the prescriber and dispensing pharmacist) on the proper use of the drug. In the OTC setting, all of these responsibilities transfer to the patient. The patient must use the information provided on the OTC drug label to decide if the drug is appropriate for his or her condition to ensure that no conditions associated with increased risk of use are present, and to use the drug properly to maximize efficacy and minimize risk. The patient may

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TABLE 1 Lovastatin OTC Label Instructions for Consumer Self-Selection and Self-Deselection*

Product may be used if:
- Men ≥45 yr of age or women ≥55 yr
- LDL cholesterol 130–170 mg/dL
- ≥1 of the following risk factors is present:
  - Smoking
  - HDL cholesterol <40 mg/dL
  - High blood pressure
  - Family history of cardiovascular disease

Do not use product without discussion with a doctor if:
- Liver disease (current)
- Pregnant or breast-feeding
- Allergic to lovastatin
- History of muscle pain, weakness, or tenderness while taking cholesterol-lowering medication
- History of cardiovascular disease (heart attack, angina, stroke)
- Diabetes
- Triglycerides ≥200 mg/dL
- HDL cholesterol >60 mg/dL
- LDL cholesterol >170 mg/dL
- Currently taking any prescription medication or other cholesterol-lowering medication

HDL = high-density lipoprotein; LDL = low-density lipoprotein; OTC = over-the-counter.
*Selection criteria were designed to identify consumers who have an approximate 10-year cardiovascular risk of 10% to 20% and who are likely to reach an LDL cholesterol target of 130 mg/dL with lovastatin 20 mg. Do-not-use criteria were based on identification of patients with low risk, or of patients with sufficiently high risk that they should receive more aggressive therapy.

discuss these issues with a healthcare professional, and the label may encourage such interactions, but the sale is not predicated on such interactions. Thus, the US Food and Drug Administration (FDA) requires that manufacturers provide evidence that a drug can be used safely and effectively in the OTC setting before such marketing can occur.[6,7]

Manufacturers have been conducting research on the OTC use of hypolipidemic drugs for ≥10 years. In 2000, the FDA's Nonprescription Drug Advisory Committee met with the Endocrinologic and Metabolic Advisory Committee to consider data on 2 potential OTC statins.[8,9] At that time, the committees recommended against OTC statin availability and identified several areas for which more data would be required before allowing a conclusion to be made regarding the safe and effective use of these drugs in an OTC setting. Examples of concerns included whether consumers could self-select for OTC statin therapy based on their cholesterol concentrations, whether a population of consumers for whom OTC statins would be appropriate could be identified, possible diversion of patients from supervised optimal statin therapy to inadequate OTC therapy, identification of an OTC statin dose that would be safe and effective, consumers' adherence to an OTC regimen over the long term, and whether consumers would self-triage to supervised care if the OTC statin did not provide adequate therapy.

Recently, a large study of lovastatin 20 mg (Mevacor; Merck & Co., Whitehouse Station, NJ) use in a simulated OTC setting was conducted.[10] The Consumer Use Study of OTC Mevacor (CUSTOM) included 3,316 consumers and concluded that consumers could safely use lovastatin and achieve the intended LDL cholesterol–lowering benefits of the drug.[10] The current article examines the data from CUSTOM in the context of understanding consumer behaviors relevant to the use of statins in an OTC setting.

PATIENTS AND METHODS

Details of CUSTOM have been published elsewhere.[10] Because it was designed to replicate an OTC setting, the conditions of the trial were as natural as possible, with minimal interference in subject decision making by study personnel. Briefly, consumers were recruited by mass media advertising for a cholesterol treatment. Interested consumers called a toll-free number and were referred to a storefront study site. At the site, the lovastatin product was displayed for potential sale. The product label indicated criteria for consumers to use the product, as well as contraindications for use (Table 1). Specifically, the label indicated that the drug should be used by individuals with an LDL cholesterol level between 130 and 170 mg/dL who had ≥1 other risk factor (smoking, high-density lipoprotein cholesterol <40 mg/dL, hypertension, or a family history of cardiovascular disease). The label indicated that use should be limited to men ≥45 years of age or women ≥55 years of age. To alert higher-risk individuals that they should not use the drug without physician approval, the label instructed consumers not to use the drug if they had liver disease, diabetes mellitus, a history of cardiovascular events, a previous history of muscle symptoms while on hypolipidemic therapy, severe hyperlipidemia, or were pregnant or breast-feeding. If the drug was purchased, the label instructed the consumer to take one 20-mg tablet per day. Consumers had the option of purchasing a cholesterol test at the study site. For study purposes, all participants had a cholesterol analysis

TABLE 2 Concordance Between Self-Reported Low-Density Lipoprotein (LDL) Cholesterol Concentrations and Measured LDL Cholesterol Concentrations in 667 Lovastatin OTC Users at Baseline*

Self-reported LDL (mg/dL)	Measured LDL Cholesterol Concentration (mg/dL)		
	<130	130–170	>170
<130	87†	16	9‡
130–170	54	250†	44‡
>170	13	26	168†

OTC = over-the-counter.

*For convenience, LDL cholesterol concentrations have been grouped into ranges. Values are number of consumers in each group.

†Groups with agreement between self-reported and measured LDL cholesterol concentrations.

‡Participants with measured LDL concentrations >170 mg/dL, but self-reported LDL cholesterol concentrations <170 mg/dL.

performed, but the results were not given to them unless they had independently purchased the test. Consumers also completed a questionnaire that provided demographic information and data relevant to their decision with respect to their lovastatin OTC purchase.

The study site storefronts remained operational so that consumers could return to purchase more OTC lovastatin and obtain follow-up cholesterol testing if desired. The label indicated that patients should obtain a follow-up cholesterol test 6 weeks after initiating therapy and, if the target LDL cholesterol of 130 mg/dL was not achieved, the consumer was instructed to discontinue OTC lovastatin use and seek follow-up from a healthcare professional. For study purposes, cholesterol testing was performed on all available patients 26 weeks after the initial lovastatin OTC purchase.

The lovastatin OTC purchase included a Consumer Assistance Program membership that provided regular newsletters on cholesterol and health issues, postcard reminders of key instructions, and the opportunity to obtain e-mail and video recordings designed to assist patients with their management of cardiovascular risk factors.

RESULTS AND DISCUSSION

A total of 3,316 consumers visited OTC lovastatin study sites and evaluated the drug for potential purchase. Of these, 1,205 consumers purchased lovastatin OTC and 1,061 of the 1,205 consumers took ≥1 dose of the drug.

CUSTOM showed that, as a group, consumers using lovastatin OTC lowered their LDL cholesterol and attained target concentrations to a degree similar to that reported in classic lovastatin clinical trials.[10] CUSTOM also provided data germane to the issue of consumer behaviors central to the appropriateness of statins for OTC use. These data will be organized and discussed in the context of questions raised in the literature and the FDA's review of OTC use of statins.

Do consumers know their LDL cholesterol? Participants in CUSTOM were asked to report their LDL cholesterol concentrations before lovastatin OTC use. In some cases, reports included information obtained from a cholesterol test purchased by the participant at the study test site. Baseline blood samples were also obtained from all lovastatin OTC purchasers, but to maintain the realistic nature of the CUSTOM design, the LDL cholesterol results from these analyses were not shared with the participants. Thus, consumers' knowledge of their LDL cholesterol status could be assessed.

Self-reported LDL cholesterol values and measured LDL cholesterol concentrations at baseline were available for 667 lovastatin OTC users (Table 2). When these estimates and measurements are compared based on relevant LDL cholesterol ranges (<130 mg/dL, 130 to 170 mg/dL, and >170 mg/dL), self-reported values and measured concentrations agreed 76% of the time (Table 2). Of most concern would be consumers with higher LDL cholesterol concentrations (and thus cardiovascular risk) than they self-recognize who thus might be diverted from more optimal care by OTC statin use. Participants had an LDL cholesterol >170 mg/dL and self-reported their LDL as lower in only 53 cases (8%). Thus, consumers who purchased and used lovastatin OTC appeared able to self-characterize their LDL cholesterol into relevant concentration bands.

Importantly, this knowledge of lipid status should not be extrapolated to the general population. Participants in CUSTOM were self-selected based on interest in treating their cholesterol and were thus also likely to be highly motivated. Purchasers also knew from the label that knowledge of their LDL cholesterol concentrations was required for proper use of lovastatin OTC. The data nonetheless support the concept that a target population of consumers with knowledge of their lipid status can appropriately self-select for use of an OTC statin, and suggest that patients without such knowledge are less likely to purchase the drug.

Do consumers make an appropriate use decision based on their risk stratification? The lovastatin OTC label contained 2 sets of instructions intended to allow self-selection of a target population for whom the drug would be clinically effective and appropriate. The first criterion was based on the consumer's LDL concen-

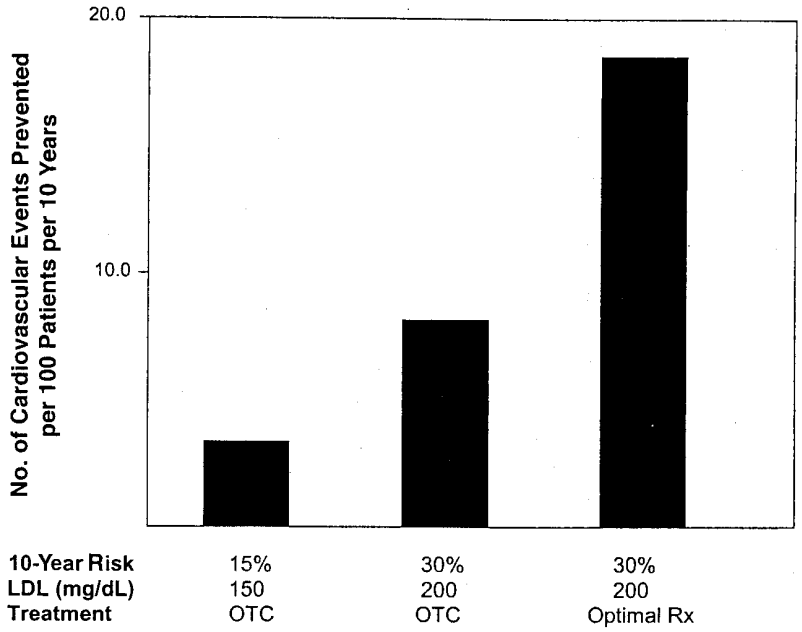

FIGURE 1. Ten-year absolute risk reduction in intermediate- and higher-risk patients as a function of low-density lipoprotein (LDL) cholesterol and treatment (Rx) received. OTC = over-the-counter.

tration and intended to facilitate treatment of consumers likely to reach target LDL cholesterol concentrations with lovastatin 20 mg/day. Measured LDL cholesterol concentrations were available for 931 of the lovastatin OTC users. Of these patients, 44% had LDL cholesterol concentrations in the 130 to 170 mg/dL target range. An additional 22% had LDL cholesterol concentrations <130 mg/dL and thus would receive relatively less absolute risk reduction from lovastatin OTC use. Of potentially more concern, 34% of the group had LDL cholesterol concentrations >170 mg/dL and thus were less likely to reach target LDL cholesterol concentrations. Therefore, those patients with more severe hypercholesterolemia might be undertreated at the 20-mg lovastatin dose.

A second set of label instructions was intended to allow self-selection of individuals with a 5% to 20% 10-year risk of myocardial infarction or death from coronary artery disease based on comorbid conditions, age, and sex. Application of the Framingham risk calculations to the self-selected lovastatin users showed that risk calculations could not be performed for 78 of the 1,059 participants. Of the remaining 981 participants, 47% had 10-year risks in the 5% to 20% range. An additional 29% had 10-year risks <5%. As with the participants with lower LDL cholesterol concentrations, these participants would have less absolute risk reduction from statin therapy. Finally, 24% had calculated 10-year coronary risks >20% or had known coronary disease, diabetes, or a history of stroke and thus would have ideally received supervised, intensive statin therapy. Interestingly, of the 233 participants in this higher-risk cohort, 97 (42%) reported using lovastatin OTC only after discussing it with their physician. This suggests that for these individuals, lovastatin OTC may be a component of supervised care rather than true diversion.

The potential impact of diversion from supervised optimal statin therapy induced by lovastatin OTC availability can be visualized by converting relative risk reductions to absolute risk reductions. Three model consumers and estimates for potential risk reduction will illustrate the principles (Figure 1). The target consumer for lovastatin may be considered someone with a 10-year event risk of 15% and an LDL cholesterol level of 150 mg/dL. Based on CUSTOM, this individual would experience an LDL cholesterol lowering of 20%.[10] This is a conservative estimate based on the largest available cohort. A 25% reduction was observed in individuals for whom fasting samples were available at both baseline and study exit.[10] Based on a randomized, primary prevention clinical trial with lovastatin, this degree of LDL cholesterol reduction can be estimated to translate into an approximately 25% reduction in cardiovascular events.[11] Given the baseline 15% risk, this would correspond to a reduction from 15 events per 100 patients to 11.25 events per 100 patients, or a net reduction of 3.75 events per 100 patients. If a higher-risk patient with an LDL cholesterol level of 200 mg/dL and a 30% 10-year risk uses lovastatin OTC, the same 20% reduction in LDL cholesterol would translate into a net reduction of 7.5 events per 100 patients, assuming a similar 25% reduction in events. In contrast, if this higher-risk patient underwent supervised care and the statin dose was titrated to meet the guidelines of an LDL cholesterol level of 100 mg/dL, there would be a 50% lowering of LDL cholesterol and as much as a 60% risk reduction.[12] For these high-risk patients who

are optimally treated, this would correspond to a net reduction of 18 events per 100 patients. Thus, in this highly idealized context, the diversion of the high-risk patients from optimal care would result in an excess of 10.5 events (18 − 7.5) per 100 patients over a 10-year period. Thus, even treatment of only 3 target consumers with lovastatin OTC who are not otherwise receiving statin therapy for each high-risk patient truly diverted from optimal care would result in a net public health benefit (3.75 events in 100 moderate-risk patients prevented times 3 patients vs 10.5 excess events in 1 higher-risk, diverted patient). Although these specific numbers are not intended to reflect the true impact of an OTC statin, they illustrate how the public health impact of diversion from optimal treatment can be conceptualized and approximated.

These simulations can be examined in the context of the CUSTOM data.[10] First, all patients using lovastatin OTC would receive some risk reduction. Thus, if the alternative is the absence of hypolipidemic therapy, the public health benefit is clear. Nonetheless, of the lovastatin OTC users in CUSTOM, only 24% (233 of 981) represented higher-risk patients, based on either a Framingham 10-year event risk >20% or a history of coronary disease, diabetes, or stroke. Thus, even if all the higher-risk patients were diverted from optimal therapy (an extremely unlikely scenario), the net public health benefit of OTC availability might still be positive based on the event reductions achieved in the higher-risk patients and the 77% of treated patients with lower risk estimates. As the higher-risk patients do experience a risk reduction with lovastatin OTC, to the degree these represent individuals who would not otherwise be treated, the public health benefit would be amplified. In CUSTOM, only 11 participants (1%) of the cohort using lovastatin OTC could be documented as substituting the product for existing prescription statin therapy. Other participants might have been using the OTC product rather than seeking supervised therapy for a number of reasons, including barriers to accessing healthcare.

Do consumers with potential clinically significant drug interactions decide not to use the OTC drug? Lovastatin may be involved in a number of drug–drug interactions, with the potential to increase plasma lovastatin concentrations.[13] The use of the 20-mg dose in the OTC setting provides a considerable margin of safety as compared with the highest approved prescription dose of 80 mg/day. Nonetheless, drug–drug interactions that increase plasma lovastatin concentrations and increase the risk of myopathy should be avoided by consumers in the OTC setting. Gemfibrozil coadministration with statins has been particularly associated with myopathy risk.[14] The association appears to result from a novel gemfibrozil effect on hepatic glucuronidation of some statins.[15,16] Thus, avoiding concomitant use of gemfibrozil or other statins would be of particular importance in the OTC setting. The lovastatin OTC label in CUSTOM incorporated warnings against use without physician consultation if the consumer was taking any prescription drugs, including any other lipid-lowering therapies. This strategy was selected to avoid reliance on the consumers' ability to recognize specific drug names on the label.

The 3,316 consumers who evaluated lovastatin OTC for purchase included 48 who were taking gemfibrozil and 609 on any lipid-lowering therapies. Of the 48 participants on gemfibrozil, 12 purchased lovastatin OTC and 10 took ≥1 dose of lovastatin OTC. Of the 10 lovastatin OTC users on gemfibrozil, 8 (80%) reported checking with their physician before using lovastatin OTC. Similarly, of the 609 participants on any lipid-lowering therapy, 184 purchased the product, and 165 took ≥1 dose. Of these 165, 109 (66%) reported checking with their physician before using lovastatin OTC.

No adverse events attributable to lovastatin were reported in the 165 participants who used lovastatin OTC while taking other lipid-lowering medications. This is consistent with the safety margin at the 20-mg lovastatin dose and the low frequency of adverse events, even when the contraindicated combinations are taken. Thus, as it is expected that some patients will not heed the label warnings, the risk must be evaluated as the frequency at which the risk behavior is observed and the risk of adverse clinical consequences if the contraindicated behavior occurs. In the case of lovastatin drug interactions, it appears that the use of interacting drugs, including other statins, will occur at frequencies as high as 10%, most often after approval by a physician. Because the risk of adverse sequelae is low, the risk posed by this fraction of nonheeding consumers is also low. Nonetheless, strategies to better communicate the warnings concerning drug interaction risks should be considered to further lower the frequency of inappropriate combination therapies. Of interest, it is unclear why physicians apparently recommended use of lovastatin OTC in conjunction with other medications that might be associated with risk.

Protease inhibitors and cyclosporine represent 2 other potentially important drug interactions with statins.[13] A total of 34 consumers taking protease inhibitors evaluated lovastatin OTC for potential use, but only 1 purchased and used the drug. Only 3 patients taking cyclosporine evaluated the drug. One patient purchased and used the product, but only after a discussion with a physician.

An important limitation to CUSTOM is the low absolute numbers of consumers with selected risk factors or contraindications identified on the label. For example, only 48 patients on gemfibrozil and 3 patients on cyclosporine were in the population that evaluated lovastatin OTC for potential purchase. These low numbers limit the precision of the estimates for the frequency at which these patients will use lovastatin OTC. Additionally, concomitant drug use was self-reported and not independently verified, and thus might underestimate actual usage. Studies focusing on purchase/nonpurchase decisions can be conducted in consumer populations enriched for special characteristics of interest (eg, use of interacting drugs), while preserving a naturalistic setting. This

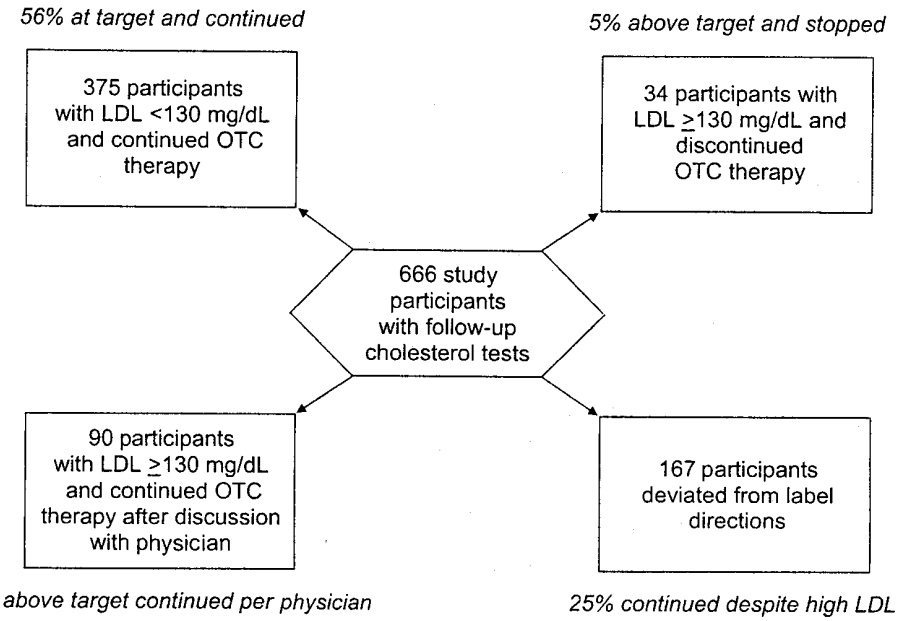

FIGURE 2. Decisions with respect to continuation of therapy made by 666 study participants receiving follow-up cholesterol testing. LDL = low-density lipoprotein cholesterol concentration; OTC = over-the-counter.

approach might allow communication of key label messages targeted to this population to be optimized.[17]

Do consumers appropriately modify their self-management based on follow-up cholesterol assessments? Titration of therapy to achieve the lowest possible LDL cholesterol concentration is critical to optimal management of hypercholesterolemia. Interpatient variability in therapeutic requirements is significant; not all patients will respond optimally to a single, fixed-dose, OTC statin regimen. Thus, it is important that patients monitor their cholesterol response to OTC therapy.

In CUSTOM, study participants could return to the study site and purchase a cholesterol blood test. Participants could also obtain a cholesterol test from any other source to which they had access. Of the 1,059 lovastatin OTC users, 116 were lost to follow-up, and thus no assessment of their subsequent testing behavior could be made. A total of 666 participants (70% of those for whom data are available) received ≥1 follow-up cholesterol test during the 26-week study period.[10] The participants who obtained tests could be characterized as making 1 of 4 decisions based on their test results: (1) obtain a test result with an LDL cholesterol <130 mg/dL and continue OTC therapy, (2) obtain a test result with an LDL cholesterol ≥130 mg/dL and discontinue OTC therapy because of inadequate benefit as per the label, (3) obtain a test result with an LDL cholesterol ≥130 mg/dL and continue OTC therapy only after consultation with a physician, and (4) obtain a test result with an LDL cholesterol ≥130 mg/dL and simply continue therapy.

As outlined in Figure 2, of the patients who had follow-up cholesterol testing, 56% of participants met the LDL cholesterol target and continued therapy, 5% stopped therapy after failing to meet the LDL cholesterol target, 13% continued therapy despite failing to meet targets after discussing the data with their physician, and 25% deviated from the label directions, primarily by simply continuing OTC therapy despite an LDL cholesterol ≥130 mg/dL. The first 3 decisions can be viewed as adhering to label directions and as replicating supervised care; 75% of participants fell within 1 of these 3 decision groups.

As would be expected, not all participants followed the label directions. Thus, it is important to understand the clinical consequences to those consumers who did not heed the directions. In all, 277 subjects, or 26% of the users for whom follow-up data are available, continued to use lovastatin OTC without obtaining a follow-up cholesterol test. The most common reasons for not getting a test included inconvenience and lack of awareness that they should obtain the test. Study exit LDL cholesterol measurements were available for 201 of the 277 patients who did not have follow-up testing as per label instructions. Of these, 111 (55%) had LDL cholesterol concentrations <130 mg/dL, a percentage very similar to the group who obtained testing.[10] Interestingly, almost half of the 277 subjects reported an interaction with their physician during the 26-week study period, suggesting that they may have had professional guidance with respect to their statin therapy. Nonetheless, it is likely that many of these 277 participants would have had LDL cholesterol concentrations >130 mg/dL and did not know they required more aggressive statin treatment. This cohort would be analogous to the initial group with higher than desired cardiovascular risk who selected to use lovastatin OTC as discussed previously. That is, they would have received some risk reduction but less than that associated with optimal therapy. This analogy also holds for the 25% of patients who did receive

testing but continued OTC therapy inappropriately. Based on the patients who did receive testing, it can be estimated that 25% of the 277 would fall into this category. Thus, it can be estimated that 3 consumers would receive the intended benefit of the OTC statin for every person who received nonoptimal treatment. This represents a worst-case risk scenario because it is likely that many of the consumers receiving OTC therapy would have received no statin rather than optimal statin therapy in the absence of the OTC option.

Do consumers maintain or initiate relationships with healthcare professionals after exposure to lovastatin OTC? A key factor in ensuring that OTC statin availability does not result in patients' preferential use of OTC statins in lieu of supervised care is maintenance of patient–physician interactions during OTC therapy. Further, use of OTC statins might encourage consumers to seek professional care for their other cardiovascular risk factors, particularly if they do not meet LDL cholesterol targets while on an OTC statin.

Questionnaire items concerning physician interactions were answered by 1,030 of the lovastatin OTC users. Of these, 635 (62%) had discussed their cholesterol levels with their physician within the previous year. This suggests that OTC statin users are likely to be more knowledgeable about cholesterol risks and more motivated to lower their risk than the average consumer. The lovastatin OTC label encouraged consumers to discuss the drug's use with their physicians. Of the 1,155 participants who purchased lovastatin OTC, 42% discussed the drug with their physician before using it. In several cases, these discussions led participants to decide that they should not use the product. In other cases, physician recommendations led participants to decide the opposite, despite relative contraindications for lovastatin OTC. For example, of the consumers with LDL cholesterol concentrations >170 mg/dL or triglyceride concentrations >200 mg/dL (label criteria for deselection), 38% discussed lovastatin OTC with their physician before use. Additionally, 22% of the 2,111 consumers who visited the study sites but did not purchase the product discussed lovastatin OTC with their physicians before making a decision with respect to purchase.

Over the course of the study, 57% of the lovastatin OTC users reported an interaction with their physician. These data suggest that OTC statin use is not associated with a discontinuation of contact by consumers with their healthcare providers. The number of patients with physician interactions during the 6-month study period was similar to the number who discussed their cholesterol levels with their physician during the year before the study. Additionally, of the 269 lovastatin OTC users who had not talked with their physician about cholesterol in the 2 years before the study, 34% reported that they discussed cholesterol issues with their physician during the study. Thus, in this highly motivated consumer population, self-management of moderate hypercholesterolemia can represent an adjunct to physician care and may facilitate increased interactions with physicians regarding cholesterol management.

As with all consumer behaviors related to OTC drug use, the frequency at which study participants interacted with physicians did not reach ideal levels. The results reported need to be considered while understanding that the population studied was not already receiving adequate treatment for hypercholesterolemia and thus represents a population with unspecified barriers to such treatment, despite their motivation as evidenced by lovastatin OTC purchase. Thus, the findings in CUSTOM that participants seem to maintain—and in some cases increase—their physician interactions are important. How these behaviors will translate to a more generalized consumer population, with more varied motivations and barriers to healthcare access, is unclear.

Do consumers adhere to therapy with lovastatin OTC? Quantitative assessment of adherence to statin therapy during the course of the trial was limited by the simulated setting in which CUSTOM was conducted. Based on the number of lovastatin OTC users who completed ≥24 weeks of treatment, persistence was estimated as 61%. Operationally, full adherence to treatment was defined as consuming between 75% and 120% of the intended tablets (calculated as 1 per day) over the period for which medication was available. Calculated in this way, 56% of the 1,059 users were adherent to lovastatin OTC therapy. Of note, the denominators for both persistence and adherence reported above included patients who discontinued therapy as per label instructions (eg, if follow-up LDL cholesterol was ≥130 mg/dL). Good adherence to lovastatin OTC was also suggested by the 20% reduction in LDL cholesterol achieved in participants for whom both baseline and 26-week tests were available.

Although these numbers may be viewed as disappointing over a 6-month study, they must be compared with values in observational studies of prescription statin therapy in which persistence ranges from 40% over 12 months[18] to a high of 80% over 18 months in the structured Veterans Administration setting.[19] The greatest discontinuation rate for prescription statin therapy appears to be in the first 6 months.[18] Persistence with statin therapy also appears to be higher in higher-risk populations,[20] in contrast to the primary prevention target in CUSTOM. Of note, the majority of participants in CUSTOM met guideline criteria for initiation of statin therapy but were not on prescription therapy. This underscores the challenge of selecting a comparator for the CUSTOM results. If the absence of therapy is used, any adherence represents a public health benefit, whereas comparisons with patients receiving supervised care at baseline are less impressive but may also be inappropriate.

Purchase of lovastatin OTC in CUSTOM was accompanied by a variety of support materials intended to ensure adherence to therapy, heeding of the label directions, and continued interactions with healthcare professionals. The degree to which these materials contributed to the adherence rates observed cannot be measured. In all, >85% of lovastatin OTC users reported using ≥1 aspect of the supporting materials (excluding the package label) over the course of the study. These materials included a dedicated Web site (accessed by 124 lovastatin OTC users) and video

material that was sent to consumers on request (used by 166 lovastatin OTC users).

CONCLUSION

Predicting consumer behavior if OTC statins become available is a challenge, but it is critical to assessing the risk–benefit ratio of such availability. CUSTOM was conducted in a natural setting to assess consumer ability to self-manage hypercholesterolemia. The CUSTOM dataset provides estimates for the frequencies at which critical consumer behaviors occur that could potentially modify the risk–benefit ratio of OTC statin availability. The results show that large numbers of consumers not currently on hypolipidemic therapy can use OTC statins safely and achieve desirable LDL cholesterol responses. Some consumers with high cardiovascular risk or more severe hypercholesterolemia will use an OTC statin, but these individuals comprised a minority of the OTC consumers studied, and appropriate self-triage to more intensive interventions occurred with high frequency. A substantial percentage of individuals at higher risk for statin-induced adverse effects heeded label warnings not to use the drug. Based on consumer behaviors quantified in CUSTOM, the probable net public health effect of OTC statin availability appears to be reduction of cardiovascular events on a population basis, even accounting for the potential of higher-risk patients to divert from intensive therapy. Most users of lovastatin OTC continued to interact with their physicians and completed therapy during the 6-month study period. These data will be valuable in future discussions of the risks and benefits of OTC statin availability because potential clinical risks associated with consumer behaviors that deviate from label directions can be compared with the potential benefit obtained from the hypolipidemic effects achieved in consumers using the drug.[20]

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Is There Value in Liver Function Test and Creatine Phosphokinase Monitoring with Statin Use?

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Statins have transformed the care of patients with vascular disease. Patients in almost every category that has been studied have benefited substantially. On the other hand, although the incidence of side effects is remarkably low, statins, like any other therapy, are not entirely free of serious risks. From the outset, based on the mechanism of action of statins, hepatotoxicity has been a concern. Moreover, although the mechanisms remain obscure, significant skeletal muscle injury, which can lead to renal failure and death, unquestionably does occur. To mitigate these risks, screening and monitoring programs for hepatic and skeletal muscle injury were put in place when statins were introduced into clinical practice. This article reviews the benefits and the costs of these efforts. Although the benefits have not been shown, the costs are real and substantial. These include the harm caused by inappropriate withdrawal of therapy, which has been shown to be life-saving, as well as the considerable financial expenditure. The conclusion that follows, based on the evidence in hand, is that although these programs were appropriate at the time statins were introduced, they are not appropriate now. ©2004 by Excerpta Medica, Inc.

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The clinical effects of statins have been exhaustively studied, and the evidence for benefit is impeccable. Vascular events have been substantially reduced in virtually all groups studied and at virtually all levels of cholesterol.[1] But no therapy is entirely risk-free, and the statins are no exception. Although rare, significant injury to the liver or skeletal muscle can occur. Therefore, screening and/or monitoring for these adverse effects have been part of the clinical protocol governing the use of statins since they were first introduced.

Statins are currently used by approximately 25 million people worldwide.[2] This widespread use constitutes a truly vast experience, and, based on this, much has been learned about the risks of statins as well as their benefits. Some changes in follow-up protocol have occurred, such as the discontinuation of routine examinations for cataracts. But screening and/or monitoring for liver and skeletal muscle injury persist. Because these practices are associated with substantial cost and consequences, it is appropriate to review the evidence supporting their use.

WHEN IS SCREENING JUSTIFIED?

The answer is not as obvious as it might appear. The objective of a screening test is not simply to accelerate recognition of a clinical problem. According to the US Preventive Services Task Force,[3] a screening test is justified only if (1) the clinical problem is significant, (2) earlier diagnosis can improve outcome, and (3) the test does not produce large numbers of false-positives or false-negatives. Does statin screening or monitoring meet these objectives?

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Statins can unquestionably provoke severe skeletal muscle damage. The possibility that statins can produce or aggravate significant hepatic injury cannot be dismissed. But these are not the issues at stake. Rather, the issue is whether the risk of these events can be significantly reduced by screening or monitoring programs. The question must be asked because these programs are neither cost-free nor risk-free, and their putative benefits must be balanced against their real costs and risks.

SCREENING OR MONITORING FOR HEPATOTOXICITY

The present labeling of statins approved by the US Food and Drug Administration (FDA) recommends that liver function tests be performed before initiation of treatment, at 6 and 12 weeks after initiation of treatment or elevation in dose, and semiannually thereafter. There are 4 hepatic syndromes to consider: asymptomatic elevation of transaminases, hepatitis, cholestasis, and acute liver failure (ALF). Each will be reviewed here; the issue of detecting preexisting liver disease will then be considered.

What is the evidence in favor of screening for asymptomatic elevation of transaminases? Screening for asymptomatic elevation of transaminases is based on the view that drugs capable of causing significant idiosyncratic hepatocellular injury are almost always associated with minor asymptomatic transaminase elevations in a substantial minority of patients.[4] Thus, minor elevations could be a marker for more serious, albeit more rare, consequences. Asymptomatic elevations of transaminases (>3 times the upper limit of normal) have been observed with all the statins, are relatively common (0.1% to 2.0%), and are dose related.[5]

But does this justify current monitoring practices? Unfortunately, it is not as widely appreciated as it

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should be that asymptomatic transaminase elevations in the absence of elevated bilirubin are not proven harbingers of significant risk.[6] Moreover, the case of the statins is complicated. On one hand, transient asymptomatic transaminase elevations may be secondary to cholesterol reduction within the hepatocytes and therefore represent a transient pharmacologic effect, not a toxic consequence. On the other hand, and more importantly, many patients who take statins have preexisting liver abnormalities that themselves produce intermittent minor asymptomatic transaminase elevations. The most common of these is nonalcoholic fatty liver disease, which is the rule rather than the exception in patients with diabetes mellitus, hyperlipidemia, and obesity.[7–10] Of course, alcohol can also commonly produce this pattern, as can any of the common viral hepatitides.

The net result is that, in the majority of patients with elevated asymptomatic transaminases who have taken statins, there is another perfectly adequate cause for the finding. This accounts for the fact that in virtually all of the clinical trials, asymptomatic transaminase elevations are as common in the placebo group as in the treated group.[11–14]

This also means that screening results in an unacceptable number of false-positives. Even assuming screening for an elevated alanine aminotransaminase was 100% sensitive and 99% specific, 98% of elevated results would be false-positives, according to calculations by Tolman.[12] False-positives can produce several adverse consequences, as outlined below.

Elevated transaminase levels are usually sporadic, not sustained, and generally return to normal with continued statin use. Moreover, they are usually not re-elevated on acute rechallenge. In addition, most elevations do not occur initially and may occur even after prolonged exposure, as would be anticipated from the complex pattern of factors that may produce these findings.[11–17] Finally, there is no evidence that significant hepatic dysfunction occurs in patients with isolated asymptomatic transaminase elevations.

Because minor asymptomatic statin-induced transaminase elevations have not been shown to be of clinical consequence and the rate of false-positives is unacceptably high, screening and monitoring for asymptomatic elevation of transaminases do not appear to be justified.

What is the evidence supporting screening and monitoring for statin-induced hepatitis or cholestasis? No cases of either hepatitis or cholestasis have been reported from any of the clinical trials. Even though each trial is limited in size, the aggregate number of patients exposed and carefully followed has grown substantially over time. This constitutes strong evidence that if these 2 side effects occur, they are very uncommon, corroborating spontaneous reports. For example, as of November 2003, 251 cases of hepatitis related to lovastatin use had been reported to the Merck Worldwide Adverse Events System database.[18] This would give a simple rate of 10.4 reports per 1 million patient-years. Because reporting is voluntary, the general rule is to multiply by 10 to achieve a more accurate estimate. However, spontaneous reports are often incomplete and contradictory, with other causes not having been excluded. Detailed review of these reports indicates that statin-related hepatitis, if it indeed occurs, does so very infrequently.[12]

The estimated rate of cholestatic reactions to statins is 1 per 153,000 patient-years.[18] In clinical practice, the transaminases, particularly alanine aminotransaminase, are used to monitor hepatic function. To detect cholestatic reactions, alkaline phosphatase and bilirubin should be measured, but they usually are not.

However, biochemical tests are not necessary to identify the problem. Patients with cholestatic reactions are symptomatic. They develop pruritus and jaundice, which bring them to medical attention before serious liver injury results. In the literature, there have been 14 reports of either hepatitis or cholestasis related to lovastatin; all patients had a favorable clinical course.[19–28]

Asymptomatic elevation of transaminases is not related to statin-induced hepatitis. The recommended tests are not adequate to diagnose cholestasis. Moreover, there is no evidence that earlier diagnosis will alter the clinical outcome. Therefore, there is no evidence to justify screening or monitoring to identify statin-induced hepatitis or cholestasis.

What is the value of screening or monitoring to reduce the risk of ALF? ALF is a major idiosyncratic adverse reaction and therefore, by definition, is not predictable. The natural background rate of ALF is estimated at 1 per 130,000 in the general population per year, whereas the rate with statins has been estimated at 0.2 per 100,000 patient-years (ie, substantially less than the background rate).[12] ALF has been reported in patients taking statins, but not every case is related to their use. There is, however, no dispute that the risk of ALF caused by statins, if it exists, is very low. As of November 2003, 25 cases of ALF potentially related to lovastatin use have been reported to the Merck Worldwide Adverse Events System database,[29] yielding a crude frequency of 1 per 1 million patient-years.

ALF is the most serious hepatic side effect of statins. However, there is no evidence that minor asymptomatic elevations of transaminases precede ALF. Moreover, even if this were the case, the clinical course of ALF is so short (ie, days) that infrequent monitoring, which occurs at intervals of several months, would be of no value. There is no evidence that the diagnosis would be accelerated or the clinical course altered. Therefore, there is no evidence supporting screening or monitoring of liver transaminases for ALF.

What is the value of screening to detect preexisting liver disease? There have been no systematic studies of statins in patients with preexisting liver disease. Moreover, such patients have almost always been excluded from clinical trials. Indeed, with significant hepatocellular disease, except for biliary cirrhosis, cholesterol levels tend to be low and therapy therefore is not indicated. Chalasani et al[30] have examined whether patients with elevated baseline liver enzymes who

were prescribed a statin (group 1; n = 342) had a higher risk of hepatotoxicity by comparing changes in their serum enzymes over 6 months with those of a group having normal serum enzyme levels at baseline who were prescribed a statin (group 2; n = 1,437) and with those of a group having elevated levels at baseline who were not prescribed a statin (group 3; n = 2,245). Group 2 had a lower incidence than group 1 of mild to moderate elevations (1.9% vs 4.7%; p = 0.002), but not of severe elevations (0.6% vs 0.2%; p = 0.2). Statin discontinuation was the same in both groups. When groups 1 and 3 were compared (the focus of the study), there were no differences in the incidence of mild to moderate elevations (4.7% vs 6.4%; p = 0.2) or severe elevations (0.6% vs 0.4%; p = 0.6). Accordingly, these data do not provide evidence of a greater risk of statin-induced hepatotoxicity in patients with preexisting liver disease. Also, Angulo[8] reported that statins do not worsen outcomes in patients with chronic transaminase elevations caused by hepatitis B or C and indeed may improve the abnormal pattern of enzyme elevation in fatty liver.

There is no published evidence that statins unfavorably affect the clinical course of established liver disease. Given the frequency with which statins have been used and the absence of published reports of adverse clinical consequence, the likelihood that statins adversely affect preexisting liver disease is low. Moreover, there is no evidence that statin-driven screening or monitoring by general physicians is an effective tool to identify previously unsuspected established liver disease.

SCREENING OR MONITORING FOR MYOPATHY OR MYOSITIS OR RHABDOMYOLYSIS

All 3 syndromes can be related to statin therapy and are distinguished as follows.[1] Myopathy refers to myalgia (eg, muscle pain, ache, muscle tenderness, or muscle weakness without any increase in creatine phosphokinase [CPK]). Myositis is characterized by muscle symptoms with increased CPK levels. The overall estimated rate of myopathy is 0.08%. But the actual frequency is related to dose and to the statin used (the risks are similar with lovastatin, pravastatin, simvastatin, and atorvastatin but are substantially higher with cerivastatin), and are increased with coadminstration of a series of other drugs, such as gemfibrozil, and in patients with complex medical problems.[1,31-34] Rhabdomyolysis is defined as muscle symptoms with marked CPK elevations (typically substantially >10 times the upper limit of normal) and with creatinine elevation. The risk of fatal rhabdomyolysis is estimated at <1 death per 1 million prescriptions.[33]

There is no FDA requirement for routine CPK screening or monitoring with statin therapy. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) has suggested CPK screening to identify the small minority of patients with elevated CPK before statin administration.[31] This recommendation is not based on evidence that these patients are at increased risk. Rather, because there are multiple causes of elevated CPK, the strategy suggested by NCEP ATP III may help reduce subsequent clinical confusion. On the other hand, it is equally possible that other causes of elevated CPK, such as strenuous exercise or hypothyroidism, may affect the subsequent samples and lead to inappropriate discontinuation of a potentially life-saving medication. The recent guidelines of the American College of Physicians for the treatment of dyslipidemias in diabetes do not recommend monitoring during statin use.[35]

Because there is no evidence that screening or monitoring of CPK will identify those patients at risk of myopathy, myositis, or rhabdomyolysis, there is no justification for screening or monitoring CPK.

If screening is not of benefit, does that mean it is without adverse consequence? False-positive tests create costs and consequences both for the patient and the healthcare system. An obvious consequence is the consternation that a patient may feel if test results indicate a possible adverse side effect. Another consequence is that if statins are stopped because of a false-positive test result, any potential benefit from therapy is lost. A myocardial infarction or a death that could have been prevented could occur. If the risk of hepatic injury based on an asymptomatic transaminase elevation is much lower than the likelihood of benefit from reduction in the risk of vascular disease, more patients will be harmed than helped.

False-positives also create financial cost, both for the patients, their employers, and colleagues, and the healthcare payment system, whether public or private. For example, let A equal the laboratory cost for all screening and monitoring tests performed per year per patient for possible hepatic and myopathic risk from statins. Assume that no additional visits are necessary for the screening or monitoring tests to be performed. Presently, there are >10 million patients on statin therapy in the United States alone.[36] Therefore, if FDA recommendations are followed, screening or monitoring will cost a minimum of $A \times \$10^7$ per year per 10 million patients treated.

In addition to these costs are the costs for following up false-positive test results. Based on the clinical trials, let us assume that 1% of all patients treated for hepatotoxicity will require follow-up for a transaminase increased >3 times the upper limit of normal. The cost of follow-up will equal the cost of the additional tests plus the professional costs for evaluating these results plus the additional costs to the patient for going to care plus the costs to society for lost productivity. Let the sum of these costs be represented by B. Accordingly, the follow-up costs of false-positive test results will be represented as $B \times \$10^5$ per 10 million patients per year. The actual cost of B will vary, but considering the elements involved, let us assume that at a minimum B will equal $10 \times A$, which is a conservative assumption. Therefore, the follow-up costs will equal $A \times \$10^6$ per 10 million patients per year.

Thus, the total costs per year for screening and monitoring equals $1.1A \times \$10^7$ per year. For the first

year, based on accepted Medicare rates, the costs for transaminases would be approximately US$60, and for 1 CPK approximately US$9. For subsequent years, this cost would decrease to US$30. Assuming a weighted cost of US$40, the minimal estimate is US$440 million per year per 10 million patients treated. Obviously, this is a crude estimate because only a fraction of the patients on statins are followed as per the guidelines. Nevertheless, whatever this fraction is and whatever the absolute size of *A*, given the number of patients who take and will take statins, the costs to the system, whether the payer is private or public, are substantial.

RISK–BENEFIT RATIO

The fact that screening and monitoring are not beneficial does not mean that statin therapy is risk-free. There is a small but real risk of significant clinical injury. This raises the issue as to whether any risk is acceptable in either the prescription or over-the-counter (OTC) setting. The short answer is that no therapy is entirely risk-free. If absolute absence of risk is an essential criterion, there will be no therapies in either setting.

For example, there is strong evidence that aspirin can reduce vascular risk if taken on a long-term basis. It has been estimated that almost one quarter of the adult American population take daily aspirin, most for cardioprotection. The US Preventive Services Task Force has approved OTC aspirin for those with >3% 5-year risk for coronary artery disease events,[37] a population in which there will be 0 to 2 aspirin-related hemorrhagic strokes and 2 to 4 major gastrointestinal bleeds over the same period—major event rates that are substantially higher than those calculated for statins.

CONCLUSION

Based on the available evidence, it appears that the screening and monitoring practices currently used to identify individuals at risk of significant hepatic or skeletal muscle injury from statins do not result in identifiable benefit for patients. They do generate enormous costs and sometimes substantial concern for the patient. They also can lead to harm if the proven benefits from statin therapy are lost because of erroneous concerns about their side effects.

The physician should be able to update his or her practice based on experience or learning. Unfortunately, many physicians are held hostage to the fear of a malpractice action if they do anything that does not strictly conform to the guidelines of their professional organizations and those of the FDA. That increases the pressure on these organizations to ensure that all their requirements and judgments remain evidence-based rather than precedent-based.

Academics can assist them in this effort by the presentation of independent updated views. Based on the evidence presented here, I conclude that routine screening and monitoring for statin side effects should be discontinued. This change should not be driven primarily by the legitimate desire for more effective use of the limited available capital resources or simply by the mathematical relation between the likelihoods of good versus adverse outcomes. Both are important considerations but are not the primary calculus that should direct us. Instead, the core reason should be our commitment to telling the truth. Bad outcomes do occur as a result of well-intentioned acts, and they always matter. However, if we do not know how to prevent serious side effects, we must declare this openly to our patients and to ourselves. Fantasy will not protect them, nor will it allow us to advise them accurately. Only our best expression of the truth will allow them to make the informed choice that is their right.

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Reclassification of Simvastatin to Over-the-Counter Status in the United Kingdom: A Primary Prevention Strategy

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Simvastatin (10-mg tablet) has been reclassified for sale as a pharmacy-only over-the-counter medicine in the United Kingdom. It is designed to be a primary prevention agent targeting that segment of the population having a moderate risk of coronary artery disease (CAD). The anticipated effect is a reduction of risk of a first major coronary event (nonfatal myocardial infarction or CAD death). Simvastatin is a component of the Heart Health Programme, which also addresses other modifiable risk factors such as diet, exercise, and smoking. Men ≥55 years of age, men aged 45 to 54 years with ≥1 risk factor, and women aged ≥55 years with ≥1 risk factor have a moderate (10% to 15%) 10-year risk of developing CAD. Risk factors include having a first-degree relative with a history of early family CAD, smoking, being overweight, and South Asian ethnicity. Simvastatin 10 mg lowers low-density lipoprotein cholesterol levels by approximately 30%, with a resultant 33% reduction in risk of a major CAD event after 3 years. After the patient completes a check-box questionnaire regarding his or her medical history and other specific risk factors, the pharmacist performs a few simple physical measurements and makes a decision as to CAD risk and simvastatin eligibility. After 1 month of simvastatin therapy, cholesterol testing is highly recommended to patients, and a kit is made available that permits home blood collection and analysis at a central laboratory.

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In the United Kingdom, coronary artery disease (CAD) remains the leading cause of death in adults. At the age of 40, the lifetime risk of CAD is 1 in 2 for men and 1 in 3 for women. In recent decades, the mortality rate for cardiovascular disease has decreased, but not the incidence rate.

Statin therapy has been proved to reduce cardiovascular morbidity and mortality in patients with hypercholesterolemia. In 2002, 1.5 million patients in England, primarily those at high risk for CAD, took statins.[1]

On May 12, 2004, Zocor Heart-Pro (simvastatin 10-mg tablet; Johnson & Johnson · MSD Consumer Pharmaceuticals, Buckinghamshire, United Kingdom) was reclassified for supply and sale as a pharmacy-only (category P) over-the-counter (OTC) medicine in the United Kingdom.[2] This decision made the United Kingdom the first country to allow the sale of OTC statins.[3] The reclassification of simvastatin is designed to be an effective public health intervention, a primary prevention agent targeting a large percentage of the moderate CAD risk population. The intended clinical effect of OTC simvastatin therapy is the reduction in risk of a first major coronary event (nonfatal myocardial infarction [MI] or CAD death).[4] Simvastatin is a component of the Heart Health Programme, which also addresses other modifiable risk factors such as diet, exercise, and smoking.

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BACKGROUND AND RATIONALE

The UK National Health Service framework has set a goal to treat individuals who have a 30% 10-year CAD or stroke risk with prescription statins. This practice is based on the Joint British Recommendations on Prevention of Coronary Heart Disease in Clinical Practice.[5] Government resources are limited; statins now cost the UK National Health Service about £700 million (US$1.3 billion) per year and are the largest expenditure in the drug budget.[6]

In 2003, the UK Department of Health announced it would encourage pharmaceutical companies to apply for the right to sell low-dosage OTC statins.[7] Solid data support statin treatment for the lower or medium CAD-risk population. The OTC prescribing policy will shift some costs to patients, but it is hoped that, through this initiative, statins will have more of a primary prevention effect on CAD than currently is the case.[8]

In the United Kingdom, there are 3 categories of medications. First, prescription-only medicine (POM) requires a physician to initiate therapy and provide follow-up; public advertisement is prohibited. Second, category P drugs are sold only from a registered pharmacy under a pharmacist's supervision. Self-selection is not permitted, as category P drugs are stored behind the counter. Labels provide detailed information on usage. Third, general sales list (GSL) medicines are sold by any lockable business (superstores, health food stores, gas stations). Self-selection is allowed.[9,10]

A 2001 British Cardiac Association survey determined that few people in the United Kingdom know their lipid measurements, and most do not have an understanding of the role of cholesterol in cardiovas-

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TABLE 1 Risk Factors

- First-degree relatives (parent or sibling) with early history of CAD; <55 yr for men, <65 yr for women
- Smoker, either current or in the past 12 mo
- Overweight (defined as BMI >25) or truncal obesity (defined as waist in men ≥40 in, in women ≥35 in)
- South Asian ethnicity, specifically Indian, Pakistani, Bangladeshi, and Sri Lankan

BMI = body mass index; CAD = coronary artery disease.

cular disease. The majority of pharmacies in the United Kingdom cannot provide adequate cholesterol testing because of space and equipment shortages, insufficient staff training, long lines, and quality control issues. These factors suggested that a large proportion of the targeted treatment group would view required cholesterol screening as a barrier to participation. However, health consumer research indicates that UK adults are motivated to reduce their risk of "heart attacks."[9]

EPIDEMIOLOGY

CAD is the etiology for 30% of all male deaths and 23% of all female deaths in Great Britain. At any age, men have a greater risk of heart disease than women. The broader category of cardiovascular disease accounts for 270,000 deaths per year.[11] On the basis of age alone, at age 55 years men in the United Kingdom have a 10% to 15% 10-year risk of CAD.

There is a direct relation between low-density lipoprotein cholesterol (LDL) level and CAD risk. Even a reduction in LDL cholesterol levels results in a lowering of risk. Statin therapy has contributed to a 23% decrease in both the MI and stroke mortality rates in people <75 years of age. A population-targeted effort to lower cholesterol levels, particularly in those people with a moderate risk for CAD, is an option to help lower cardiovascular disease incidence rates. Among the benefits are decreased rates of sudden death and fatal MI, fewer coronary disease hospitalizations, fewer revascularization procedures, and decreased costs of secondary prevention drugs.[12] Lower cholesterol levels can also ameliorate the adverse effects of diabetes mellitus, hypertension, and smoking.

In the United Kingdom, the average total cholesterol level is 5.8 mmol/L (224.5 mg/dL) for men >45 years of age and 6.2 mmol/L (239.9 mg/dL) for women >55 years of age. A meta-analysis of short-term studies with simvastatin 10 mg indicates an LDL cholesterol reduction of 1.3 mmol/L (50.7 mg/dL), with a 95% confidence interval of 1.22 to 1.40. The mean pretreatment LDL cholesterol level is 4.8 mmol/L (185.8 mg/dL).[13] Therefore, LDL cholesterol decreased about 27%. This improvement in LDL cholesterol reduces the risk of a major coronary event (nonfatal MI or CAD death) by 33%.

CORONARY ARTERY DISEASE RISK DETERMINATION AND OVER-THE-COUNTER SIMVASTATIN

Simvastatin 10 mg, marketed as Zocor Heart-Pro, category P medication will be sold to the moderate CAD risk patient population. Physicians with expertise in lipids, cardiovascular disease, and primary care provided important input into the decision to create a pragmatic model and treatment strategy for this risk group. Self-reported risk factors are emphasized to assess the level of risk; pretherapy cholesterol testing is not a requirement for treatment. An approximate 30% reduction in LDL cholesterol level will result in an 11% diminution in risk of a major CAD event after 1 year of therapy, 24% after 2 years, and 33% after 3 years.[13] There is evidence that patient adherence to statin therapy decreases to as low as 25% after 5 years.[14]

What is the process by which individuals are determined to be at moderate risk for CAD? Age is the primary variable that determines CAD risk; increasing age results in greater risk. Age-specific population means for diastolic and systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol levels are available from 2 surveys (the 1990 Dietary and Nutritional Survey[15] and the 1998 Health Survey for England: Cardiovascular Disease[16]). Using these data, a software application, Cardiac Risk Assessor V98.02 (University of Manchester, Manchester, United Kingdom), was used to calculate age-specific baseline CAD risk.[9]

The Joint British Guidelines as well as the medical literature identify additional risk factors for CAD (smoking, overweight status, family history of early CAD, and South Asian ethnicity). Being overweight, having a family history of early CAD, and South Asian ethnicity each increase the risk by a factor of 1.5, while smoking increases the 10-year CAD risk by 5%. When each risk factor is entered into the Cardiac Risk Assessor program, age-specific 10-year CAD risk assessments are calculated for each risk factor for both men and women. Individuals at moderate (10% to 15%) 10-year CAD risk are men ≥55 years of age, men 45 to 54 years of age with ≥1 risk factor, and menopausal women ≥55 years of age with ≥1 risk factor (Table 1).[9]

There have been >73 million patient-years of statin therapy. Simvastatin in particular has very good safety and tolerability data at doses ranging from 5 to 80 mg. No routine blood monitoring other than lipid profiles is required during treatment.

Patients with a history of liver disease or known abnormal liver function tests are excluded from simvastatin therapy. Other ineligible patients include those with a history of angina, previous MI or stroke, peripheral vascular disease, diabetes, hypertension, or

familial hyperlipidemia.[17] Patients with a history of hypothyroidism, renal failure, or familial muscle disorder should consult a physician because these diseases increase the risk of muscle side effects on simvastatin therapy.

Simvastatin has a product label and patient information leaflet that are clear and complete regarding cautions and possible side effects. Drug interactions are discussed; patients are urged to consult a physician first if their daily alcohol intake exceeds 4 units for a man or 3 units for a woman. A unit is a shot of 1.5 oz (45 mL) of liquor, a half pint of beer (235 mL), or 4 oz (120 mL) of wine.[9] Detailed warnings are provided regarding the signs and symptoms that may indicate the onset of obstructive liver damage or myopathy. For either scenario, patients are instructed to stop taking simvastatin and seek medical attention. Ingestion of >1 L/day of grapefruit juice will increase the blood level of simvastatin and augment the risk of muscle side effects.

Approximately 1 month after the onset of treatment, cholesterol testing is strongly recommended to patients to determine progress in LDL cholesterol reduction, to provide motivation, and to identify those patients who are inadequately treated. For this purpose, the Heart-Pro cholesterol testing kit is to be made available for purchase at all pharmacies. Using this kit, the patient performs a finger-stick blood collection at home and mails it to a central laboratory that meets quality-control standards.[9] The full lipid profile results are mailed to the patient and, if the patient wishes, to the physician.

A database will be maintained that provides educational materials and special offers to the patient as part of an overall program designed to encourage adherence to simvastatin treatment, exercise, a low-fat diet, weight loss, and smoking cessation. If the on-treatment LDL cholesterol level exceeds 3.5 mmol/L (or 135.5 mg/dL), the patient will probably benefit from physician referral.

PHARMACIST ROLE

Pharmacists in the United Kingdom are very supportive of the reclassification of simvastatin to category P status.[18] In the National Health Service system of care, where resources are limited and 2-week waits to see a primary care physician are not uncommon, pharmacists are a valuable resource for patients who rely on self-management of some of their illnesses. World Health Organization (WHO) statistics indicate that there are 164 physicians per 100,000 population in the United Kingdom compared with the US rate of 279 physicians per 100,000 population.[19] Pharmacists in the United Kingdom have experience in providing advice to patients on the self-treatment of chronic diseases, such as eczema, arthritis, and irritable bowel syndrome, in addition to expertise in folic acid prophylaxis of neural tube defects during pregnancy and emergency contraception, which were approved for OTC sale.[4,18]

With input from pharmaceutical professional organizations in the United Kingdom, a training program for the supply and sale of simvastatin has been developed for pharmacists and their assistants. With or without assistance from the pharmacist, the patient will first complete a 1-page check-box questionnaire regarding his or her medical history and other specific risk factors. Following a discussion with the patient, the pharmacist will consult a simple nomogram to assess whether the patient is overweight and will measure the blood pressure if this has not been recently checked. A decision will then be made about the patient's CAD risk and eligibility for simvastatin 10 mg therapy.

With the first OTC simvastatin purchase, a user card will be given to the patient that is stamped and dated by the issuing pharmacist. The presentation of this card at later visits will facilitate the monthly refill for both patient and pharmacist.

APPROVAL PROCESS

In November 2003, Johnson & Johnson · MSD Consumer Pharmaceuticals submitted an application to the Medicines and Healthcare Products Regulatory Agency's (MHRA) Committee on Safety of Medicines (CSM) requesting the reclassification of simvastatin 10 mg (Zocor Pro-Heart) to OTC category P status.[20] The CSM is an expert group that provides advice on the safety, quality, and efficacy of medications, and it is also responsible for postmarketing surveillance of possible adverse drug reactions. Physicians and pharmacists report these events using the Yellow Card Scheme, a system for early detection of drug safety hazards and routine monitoring of all medicines in clinical use and reports of suspected adverse reactions.[21] Information is entered into the Adverse Reactions On-line Information Tracking System (ADROIT; MHRA, London, United Kingdom).

On November 17, 2003, the MHRA and the Health Minister announced a 9-week consultation period seeking comments from the public and stakeholders on the proposed reclassification. At its completion, on January 16, 2004, 100 submissions had been received by the MHRA.[19] None raised any significant new issues. In March 2004, the CSM met to discuss the results of the consultation and advised the ministers that simvastatin 10 mg category P medicine could be safely dispensed by a pharmacist. On May 12, 2004, the ministers approved reclassification.[2]

An editorial in the May 22, 2004, issue of *The Lancet*[22] criticized the reclassification on the grounds that trials of OTC statins for primary prevention of heart disease had not been conducted, and that data were lacking on patient adherence to OTC statin therapy. It did, however, cite a 2003 review of simvastatin 10 mg versus placebo data that showed a 27% reduction in LDL cholesterol levels, although some studies were short-term and others included CAD patients. The editors concluded that the UK government's primary reason for reclassification is financial. Reclassification restrains the rise in UK National Health Ser-

vice statin expenses by shifting some costs to patients. This shift will increase inequities in access to these medications. A surveillance system is recommended to gather data on the benefit and risk in the simvastatin patient population.[19]

THE UNITED STATES OVER-THE-COUNTER STATIN MODEL

In preparation for the 2004 New Drug Application to the US Food and Drug Administration (FDA) for OTC Mevacor 20 mg (lovastatin; Johnson & Johnson · Merck Consumer Pharmaceuticals, Fort Washington, PA) has conducted the Consumer Use Study of OTC Mevacor (CUSTOM), an actual-use study of >10,000 people.[23] CUSTOM was a 6-month study performed in a simulated retail setting, where patients recruited by advertising completed a check-box questionnaire to evaluate their own CAD risk and then purchased their medication. Optional cholesterol testing was available. Preliminary results were positive. Most participants consulted their healthcare providers, used the medication correctly, and achieved improved diet and exercise behaviors.

Also cited by Johnson & Johnson · Merck is the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a primary prevention trial in which lovastatin doses of 20 mg and 40 mg achieved a reduction in the risk of acute coronary events in a population with lipid levels comparable to the UK and US OTC target populations.[24,25]

In the United States, as in the United Kingdom, there is enthusiasm among consumers for this switch, as well as support from physicians and pharmacists. What are the similarities and differences between the UK and US models?

In both models, the statin would be sold in pharmacies. Easy-to-understand materials would help patients assess their own eligibility for low-dose statin therapy. Both models are designed to encourage a well-trained pharmacist to corroborate this decision.

In the United Kingdom, the patient must present a user card as proof of eligibility to obtain a refill of simvastatin. Simvastatin is stored behind the counter, and the pharmacist must be consulted before the drug is dispensed. In the United States, the patient would not need to consult a pharmacist to select OTC lovastatin. In the United Kingdom, a patient may have to wait ≥2 weeks to see a primary care physician, so the pharmacist is a more readily available source of information on statin therapy and its role in reducing CAD risk. In the United States, more patients indicate that they would first discuss this issue with their physician. US consumers will need to know their cholesterol levels before they can start taking OTC lovastatin.[26]

During an interview with *The Tan Sheet*, cardiovascular medicine physicians expressed the opinion that low-dose OTC statins will benefit moderate-risk patients who are not already taking statins. Of concern are the high CAD risk patients who require high-dose statin therapy but instead choose the low-dose OTC option. UK simvastatin data on the number of patients enrolled and their on-therapy lipid levels will be of value to the FDA in its decision process.[27]

CONCLUSION

The simvastatin category P medicine pragmatic model and treatment strategy has a good opportunity to become widely used and effective in the United Kingdom because of historical, medical system, and cultural factors. Community pharmacists are proactive, are experienced in OTC treatments of chronic diseases, and have established strong relationships with local health consumers who, by necessity, are skilled in self-management of illness.

A discussion of ethics lends support to a more widespread availability of low-dose statins. The statins are safe and effective. If a category of patients is very likely to benefit from a reduction in LDL cholesterol levels by statin therapy, then OTC simvastatin should be available to them at low cost and with barriers to access removed. Patients who have received the proper information should be able to make an informed choice.

The reclassification of simvastatin 10 mg to OTC category P medicine status targets the moderate or 10% to 15% 10-year CAD risk population in the United Kingdom. If these patients also take additional steps, such as improving their diet, increasing their exercise levels, and stopping smoking, it is anticipated that they will benefit from a reduction in their risk of a first major coronary event. Another anticipated goal of this primary prevention effort is a decrease in cardiovascular incidence rates, certainly a much needed benefit for society.

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NOTES

Expanding Primary Prevention Efforts:

Allowing Consumers Access to

Over-the-Counter Statins

CME Assessment Test and Evaluation Form

Release Date: November 4, 2004 Date of Last Review: May 1, 2004 Expiration Date: November 4, 2006

CME ASSESSMENT TEST

Expanding Primary Prevention Efforts: Allowing Consumers Access to Over-the-Counter Statins

Please circle the correct answer to each question on the Answer Sheet provided. There is only one correct answer for each question.

1. Studies have documented changes in the incidence of acute myocardial infarction (MI) from the late 1970s to the mid 1990s. These changes were
   a) significant and continued decreases in the rate of acute MI over the study period
   b) sizable initial decreases in the rate of acute MI over a period of several years with no further decrease in the incidence of MI later on
   c) initial increases in the incidence of acute MI that decreased over time
   d) none of the above

2. Populationwide epidemiology studies, such as the National Health and Nutrition Examination Survey (NHANES), which was conducted from 1988 to 1994 and from 1999 to 2000, and the Minnesota Heart Study documented the epidemiology of hypercholesterolemia in the United States. These studies showed that
   a) mean cholesterol levels, when adjusted for age and stratified by sex, did not significantly change over a 10-year period (from 1990 to 2000)
   b) no significant changes occurred in age- and sex-stratified subgroups, except in men aged ≥ 75 years
   c) from 1980 to 1992, total cholesterol levels decreased in men and women
   d) no further decreases in total cholesterol were observed from 1990 to 1997, despite a concurrent increase in lipid-lowering drug prescriptions
   e) all of the above
   f) none of the above

3. Among persons with hypercholesterolemia, only about 40% are aware of their condition, <15% said they take cholesterol-lowering medication, and only 7% had a cholesterol level <200 mg/dL.
   a) True
   b) False

4. In light of the increase in cholesterol-lowering drug prescriptions, the changes in the incidence of coronary artery disease (CAD) and changes in cholesterol levels over the last 3 decades suggest that
   a) a treatment gap exists between the degree of the detection of hypercholesterolemia and the management recommended and that which is actually provided
   b) additional strategies are needed to promote primary prevention of CAD
   c) based on the distribution of the 10-year risk of MI or CAD death, 25% to 50% of adults aged ≥45 years are at moderate (10% to 20%) risk for CAD over 10 years; because this population is expected to contribute a sizable portion of CAD cases, risk reduction in this group should be part of any strategy to reduce the incidence of CAD
   d) all of the above
   e) none of the above

5. What percentage of Americans have a known risk for cardiovascular disease based on low-density lipoprotein (LDL) cholesterol levels ≥ 130 mg/dL?
   a) 12%
   b) 31%
   c) 46%
   d) 87%

6. The National Lipid Association (NLA) survey results indicate that physician-reported barriers to prescribing a cholesterol-lowering medication to untreated moderate-risk patients were
   a) patient fear of side effects
   b) cost of treatment
   c) reluctance to take prescription medications
   d) poor adherence to cholesterol-lowering treatments
   e) a and c
   f) b and d
   g) all of the above

7. Almost 90% of physicians agreed that patients with a moderate risk for CAD are candidates for cholesterol-lowering drug therapy, and nearly 80% agreed that there are many people whose moderate risk for CAD is not being treated. Why do physicians think these individuals are not being treated with cholesterol-lowering drug therapy?
   a) these patients are unaware of the risks of high cholesterol
   b) physicians give priority to lifestyle modification over drug treatment
   c) patients prefer over-the-counter (OTC) drugs

d) physicians do not have enough time to discuss high cholesterol during office visits
e) priority is given to acute symptomatic conditions over the prevention of potential chronic disorders
f) all of the above
g) none of the above

8. When asked about the most effective therapy for preventing CAD in patients who are at moderate risk, the NLA survey indicated that physicians rated cholesterol-lowering medications highest, above other approaches that included managing other CAD risk factors, taking aspirin, weight loss, and increased exercise.
a) True
b) False

9. The NLA survey asked consumers, physicians, and pharmacists if they would be interested in learning more about an OTC statin if the US Food and Drug Administration (FDA) approved one; it also asked whether consumers would purchase OTC therapy. Which of the following findings is true?
a) More pharmacists and consumers than physicians were interested in learning more about an OTC statin.
b) Consumers in the moderate-risk group, who are potentially best suited for OTC statin therapy, expressed greater interest in learning more about OTC statins compared with consumers at high risk for CAD.
c) More moderate-risk than high-risk consumers indicated a high likelihood of purchasing OTC statin therapy.
d) Pharmacists were more likely than physicians to support consumers in the decision to purchase OTC statin therapy.
e) All of the above
f) None of the above

10. A strong majority of consumers indicated that they
a) would not consult with their physician or other healthcare professional before buying OTC statin therapy
b) would talk with their physician or other healthcare professional before purchasing OTC statin therapy
c) would seek the advice of other patients before buying an OTC statin
d) none of the above

11. Which of the following issues was not a concern of the physicians and pharmacists in the NLA survey?
a) Patients discontinuing prescription lipid-lowering therapy without talking to their physicians
b) Adequacy of low-dose statins to provide benefit
c) Potential drug interactions and side effects
d) Patient ability to successfully self-manage their use of OTC statin therapy

12. It is likely that the support of pharmacists will be needed if OTC statin therapy is to be successful in the primary prevention of CAD. Within this context, and based on the NLA survey results, which of these responsibilities might not be a part of the pharmacists' role?
a) Answering patient questions and providing advice about OTC statin therapy
b) Referring patients to physicians for risk-factor management
c) Monitoring lipid levels over the course of the patients' therapy
d) Helping patients determine whether OTC statin therapy is correct for them

13. The Consumer Use Study of OTC Mevacor (CUSTOM) helped define consumer behaviors in the setting of OTC statin therapy. Based on the results of this study, which of the following statements about consumers' knowledge of their own LDL cholesterol levels is true?
a) Consumers were reluctant to report their baseline LDL cholesterol levels.
b) Consumers' self-reported LDL cholesterol levels agreed with measured concentrations >75% of the time.
c) Consumers' self-reported LDL cholesterol levels agreed with measured concentrations <25% of the time.
d) In all, <10% of consumers who had an LDL cholesterol level >170 mg/dL self-reported lower levels of LDL cholesterol, thus potentially diverting themselves from more optimal care.
e) a and c
f) b and d
g) None of the above

14. In the CUSTOM study, the OTC statin label specifically indicated that Mevacor OTC (lovastatin) should be used by patients with LDL cholesterol levels between 130 and 170 mg/dL plus 1 additional CAD risk factor. The label also provided instructions to allow self-selection of patients with a moderate risk of CAD. According to these instructions, the study found that more patients made an appropriate rather than inappropriate decision about use of the drug.
a) True
b) False

15. The CUSTOM study participants who received a test result could make 4 basic decisions about their therapy based on their LDL cholesterol level: (1) achieve an LDL cholesterol level <130 mg/dL and continue therapy; (2) achieve an LDL cholesterol level >130 mg/dL and discontinue therapy; (3) achieve an LDL cholesterol level

>130 mg/dL and continue therapy only after talking to their physician; and (4) achieve an LDL cholesterol level >130 mg/dL and simply continue therapy. What percentage of patients was considered adherent to label directions (i.e., made decisions 1, 2, or 3)?
a) 25%
b) 50%
c) 75%
d) 99%

16. What percentage of CUSTOM study participants who purchased Mevacor OTC discussed the drug with their physician before they used it?
a) 10%
b) 22%
c) 42%
d) 62%

17. Which of the following statements is true?
a) Asymptomatic elevations of transaminases have been associated with all the statins, are relatively common, and are dose related.
b) Asymptomatic transaminase elevations in the absence of increased bilirubin levels are not proven harbingers of significant risk.
c) Preexisting liver abnormalities can produce asymptomatic transaminase elevations; these elevations are commonly due to nonalcoholic fatty liver disease or alcohol use.
d) Asymptomatic transaminase elevations are as common in the placebo groups as in the treatment groups in nearly all clinical trials of statin therapy.
e) Even under optimal conditions, 98% of elevated transaminase results may be false-positives.
f) All of the above
g) None of the above

18. Hepatitis and cholestasis have not been reported in any statin clinical trial.
a) True
b) False

19. Acute liver failure (ALF) is the most serious side effect of statin therapy. The rate of ALF in patients taking statins is estimated at 0.2 per 100,000 patient-years. How does the rate of ALF in the general population compare with the rate of ALF in patients taking statins?
a) The rate of ALF in the general population is lower than the rate in patients taking statins.
b) The rate of ALF in the general population is higher than the rate in patients taking statins.
c) There is no statistical difference between the rate of ALF in the general population and the rate of ALF in patients taking statins.

20. Myopathy, myositis, and rhabdomyolysis are related to statin therapy. Creatine phosphokinase (CPK) elevations can be related to muscle damage. Which of the following statements about these syndromes is true?
a) CPK levels are markedly increased in each syndrome.
b) The FDA requires routine CPK screening or monitoring with statin therapy.
c) The American College of Physicians recommends monitoring CPK levels during statin therapy in patients with diabetes mellitus.
d) All of the above
e) None of the above

21. In the United Kingdom, CAD accounts for what percentage of all deaths?
a) 10% for men and 13% for women
b) 30% for men and 23% for women
c) 60% for men and 32% for women
d) At 40%, the number of deaths attributed to CAD is almost equal for men and women

22. Simvastatin is now reclassified in the United Kingdom as a pharmacy-only OTC medicine. What drug dose does the reclassification affect?
a) 5 mg
b) 10 mg
c) 20 mg
d) 40 mg
e) 80 mg

23. The UK National Health Service requires cholesterol testing about 1 month after starting use of OTC statin therapy.
a) True
b) False

24. Consumers in the United Kingdom can purchase Zocor Heart-Pro (simvastatin) from which of the following sources?
a) Online from registered Internet health food stores
b) In person at registered health food stores
c) From a registered pharmacy without the pharmacist's supervision
d) From a registered pharmacy under the pharmacist's supervision
e) All the above
f) None of the above

CME ASSESSMENT TEST ANSWER SHEET

Release Date: November 4, 2004 **Expiration Date:** November 4, 2006

INSTRUCTIONS
To receive free CME credit (refer to the Accreditation Statement and Designation of Credit in the front of this issue), 1) read the educational objectives, review the activity, and complete the CME Post-Test; 2) record your responses on the Answer Sheet below; 3) return the completed Answer Sheet and Evaluation Form to:

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Answer Sheet (circle the best correct answer)

1. a b c d	7. a b c d e f g	13. a b c d e f g	19. a b c
2. a b c d e f	8. a b	14. a b	20. a b c d e
3. a b	9. a b c d e f	15. a b c d	21. a b c d
4. a b c d e	10. a b c d	16. a b c d	22. a b c d e
5. a b c d	11. a b c d	17. a b c d e f g	23. a b
6. a b c d e f g	12. a b c d	18. a b	24. a b c d e f

CUT HERE

REGISTRATION SHEET

I have read the articles on the "Expanding Primary Prevention Efforts: Allowing Consumers Access to Over-the-Counter Statins," published as a supplement to The American Journal of Cardiology, and have answered the CME test questions and completed the Evaluation Form for this educational activity.

CME CREDIT VERIFICATION

I verify that I have spent _____hours to complete this CME activity (not to exceed 10 hours).

Signature _____ Date _____

Last name

First name MI Degree

Specialty

Address

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Phone _____ Fax _____ E-mail_____

Date of Participation Month _____ Day _____ Year _____

Affiliation

CME EVALUATION FORM

Please rate the overall course on a scale of 1 to 5, with 1 the lowest and 5 the highest.

1. Did the material adequately describe the current trends in the management of cholesterol levels among US adults? 1 2 3 4 5

2. Did the material clearly identify the current cholesterol treatment gap? 1 2 3 4 5

3. How well did the material clarify the results of the National Lipid Association survey regarding physician and consumer attitudes about cholesterol management and over-the-counter (OTC) statins? 1 2 3 4 5

4. Did the material enable you to assess consumers' ability to safely and effectively self-manage their cholesterol? 1 2 3 4 5

5. How well did the material enable you to evaluate the need for liver function tests and creatine phosphokinase monitoring with statins? 1 2 3 4 5

6. Did the material adequately discuss the approval of OTC statins in the United Kingdom? 1 2 3 4 5

7. Will the information presented in this supplement be useful in your practice setting?

_____ Yes _____ No Comments:_____

_____

_____

8. Did you find the information presented to be objective, balanced, and free of commercial bias?

_____ Yes _____ No Comments:_____

_____

_____

9. When you receive literature that is accredited for AMA/Physician Recognition Award CME versus literature that is not accredited for CME, which are you more likely to review?

_____ CME _____ Non-CME _____ Does Not Matter

10. Do you have any recommendations to improve this program?

_____ Yes _____ No Comments:_____

_____

_____

11. What other subject areas would you suggest for course presentations?

_____

_____

_____

_____

_____

PIVOTAL LABEL COMPREHENSION STUDY SUMMARY

Background, Objectives and Method

The revised treatment paradigm for lovastatin 20 mg, developed with guidance from the FDA following the Not-Approvable Letter in October 2000, led to revisions of the package label. From October 2000 until June 2003, the label was subjected to a series of qualitative and quantitative consumer studies, with each one incorporating the learning from the prior studies on both the structure and contents of the label itself as well as changes in the survey instrument. Many of the changes that were made to the survey instrument also benefited from FDA input. The culmination of this effort was the fielding of the Pivotal Label Comprehension Study in June 2003.

The primary objective of the Pivotal study was to determine the percent of respondents who demonstrate that they comprehend the MEVACOR™ OTC package label by being able to correctly answer questions about specific elements as well as apply their understanding to "scenarios" that combine multiple elements. Secondary objectives focused on self-selection as well as the evaluation of results among low literacy and non-Caucasian subgroups. This was a one-cell study, with 696 representative respondents chosen randomly in 25 geographically and demographically dispersed malls, as well as an additional 92 respondents augmented for low literacy. Participants were screened to be cholesterol-concerned and neutral to positive on the general concept of an OTC cholesterol-lowering product called MEVACOR™ OTC. They reviewed the package label and then answered comprehension and self-selection questions.

Results

In general, respondents in the MEVACOR™ OTC Pivotal Label Comprehension Study demonstrated that they understood the key messages that were being communicated. They showed that they were able to use the label information effectively to choose appropriate next steps for a wide variety of hypothetical individuals who were presented to them via scenarios, notably those that focused on safety cautions and warnings. Also, on most of the key measures, the low literacy and non-Caucasian subgroups did not score significantly lower than their comparison groups.

In Table 1, a respondent was "correct" or "acceptable" if he or she indicated that the hypothetical person with the listed condition should talk to a doctor before using the product or not use it at all ("correct" was defined by label text specific to each condition). An "incorrect" response for these questions was that the person being described could go ahead and use the product right away. Table 1 shows that in all cases except for a scenario on Triglycerides, the correct plus acceptable scores exceeded 90%, for the total representative sample and all subgroups. Scores for Triglycerides were 80% or higher.

Table 1
Medical Condition Scenarios
Correct plus Acceptable Responses

	Total		Caucasian		Non-Caucasian		Non-Low Literacy		Low Literacy*	
Sample Size (Avg. 2 sub-cells**):	N=348		N=243		N=104		N=293		N=102	
	N	%	N	%	N	%	N	%	N	%
				A		B		C		D
Pregnant	342	(99)	242	(99)	97	(98)	279	(99)	113	(98)
Breast feeding	339	(97)	235	(97)	103	(95)	294	(97)	83	(94)
Stroke a few yrs ago	341	(97)	235	(97)	105	(97)	295	(97)	82	(93)
Heart attack last yr	320	(93)	227	(93)	90	(91)	260	(92)	106	(92)
Diabetes	340	(99)	240	(99)	97	(98)	279	(99)	110	(96)
Triglycerides 450	301	(86)	209	(86)	92	(85)	262	(86)	70	(80)
Liver disease	348	(99)	240	(99)	107	(99)	300	(99)	88	(100)c

*Includes augmented respondents.
**Respondents were divided into 2 subgroups for this series of questions. Each respondent saw 3 or 4 of the 7 possible medical conditions. Although the average sample size is noted in the table, calculations in the table were based on actual sub-cell sample sizes (e.g., rep N = 351 or 345).
Statistical significance tested in Columns A vs. B and C vs. D. Capital letters indicate differences at the 95% c.l., and lower case letters indicate differences at the 90% c.l.

In the case of hypothetical individuals taking prescription medications, shown in Table 2, respondent scores were even more positive, as all but one "correct" score exceeded 90%. This indicates a strong understanding that someone who is on a prescription medication should talk to a doctor first before using the product. For this table, only the "correct" scores are shown, since the respondents had a choice of only two responses (talk to a doctor or use right away).

Table 2
Medication Scenarios
Correct Responses

	Total		Caucasian		Non-Caucasian		Non-Low Literacy		Low Literacy*	
Sample Size:	N=696		N=485		N=207		N=585		N=203	
	N	%	N	%	N	%	N	%	N	%
				A		B		C		D
Rx for cholesterol	660	(95)	464	(96)	192	(93)	559	(96)	190	(94)
Rx for ulcer	659	(95)	458	(94)	197	(95)	560	(96)D	179	(88)
Rx for infection	639	(92)	443	(91)	192	(93)	540	(92)	184	(91)

*Includes augmented respondents.
Statistical significance tested in Columns A vs. B and C vs. D. Capital letters indicate differences at the 95% c.l., and lower case letters indicate differences at the 90% c.l.

In addition to demonstrating comprehension of the key messages, respondents were also asked whether or not they themselves could start using the product. The evaluation of these responses was based on self-reported medical histories that were collected later in the questionnaire. Table 3 shows that 90% of respondents in the total sample made a correct or acceptable self-selection decision. Because this study was conducted in malls, where respondents did not have access to their cholesterol levels or other medical history facts, the appropriate response for most people was that they should not use the product (without talking to a doctor or obtaining their cholesterol values). Therefore, "talk to doctor" was considered an acceptable response.

Of the 90% correct or acceptable responses, 66% of representative sample respondents were not appropriate (per label definition and their medical history) to start using right away, and they said so in their responses. There were also 3 respondents who were appropriate in all respects and indicated they could start using it. An additional 24% said they could start using it or they did not know if they could, but they would talk to a doctor. Finally, 10% gave a response that was considered incorrect. All subgroups showed similar strong scores.

Table 3
Whether Respondent could Begin Using Mevacor OTC Today

	Total		Caucasian		Non-Caucasian		Non-Low Literacy		Low Literacy*	
Sample Size:	N=696		N=485		N=207		N=585		N=203	
	N	%	N	%	N	%	N	%	N	%
				A		B		C		D
Correct + Acceptable	629	(90)	438	(90)	187	(90)	527	(90)	186	(92)
Correct	464	(67)	326	(67)	135	(65)	394	(67)	136	(67)
Respondent qualifies and said can use	3	(<1)	3	(1)b	0	(0)	3	(1)d	0	(0)
Respondent does not qualify and said cannot use	461	(66)	323	(67)	135	(65)	391	(67)	136	(67)
Acceptable	165	(24)	112	(23)	52	(25)	133	(23)	50	(25)
Respondent does not qualify, says can use but volunteered talking to a doctor	147	(21)	96	(20)	50	(24)	117	(20)	46	(23)
Respondent did not know if can use but volunteered talking to a doctor	18	(3)	16	(3)B	2	(1)	16	(3)	4	(2)
Incorrect	67	(10)	47	(10)	20	(10)	58	(10)	17	(8)
Respondent said can use and did not mention talking to a doctor	59	(8)	42	(9)	17	(8)	52	(9)	15	(7)
Respondent did not know if can use and did not mention talking to a doctor	8	(1)	5	(1)	3	(1)	6	(1)	2	(1)

*Includes augmented respondents.
Statistical significance tested in Columns A vs. B and C vs. D. Capital letters indicate differences at the 95% c.l., and lower case letters indicate differences at the 90% c.l.

Conclusions

These results show that respondents were able to use the label information effectively to choose appropriate next steps for a wide variety of hypothetical individuals who were presented to them via scenarios, as well as for themselves. In addition to the data provided above, the following measures were noteworthy in terms of eliciting strong scores from respondents:

- "Correct" scores of 90% or higher on the following measures:
  - Having a cholesterol test prior to starting use;
  - Taking one tablet per dose; and
  - Dosing once a day.
- Many "correct plus acceptable" scores over 90% on the following measures:

    - Complex initial usage scenarios, involving age, gender and medical information; and
    - Understanding the circumstances when one should stop using the product due to a medical condition or a new medication.
- A high level of appropriate responses on the following measures:
    - The condition that the product would be used for;
    - The product's active ingredient;
    - The best time of day to take product; and
    - Having a follow-up test at 6 weeks.

The study also highlighted several messages that were not as well communicated:

- The appropriate action steps to take if the follow-up LDL goal is not met;
- The impact on cholesterol of stopping product use; and
- The need to fast before getting tested.

Relationship of Pivotal Label Comprehension Testing to CUSTOM

Label comprehension testing is a critical input in label development but its value in predicting the choices that consumers will make in a trial that includes an actual purchase opportunity, such as CUSTOM, is somewhat limited. The two types of studies differ in many respects, notably with regard to the types of people who participate and the nature of the task they are asked to do. Given the differences between these studies, it would not be surprising to see disparate results. However, in this case, many of the results were similar or complementary. The most significant of these similarities were in the following areas:

- Physician Interaction: Substantial reliance on physician input was apparent in both studies, showing that participants understood that this new type of product is for a serious condition and has complex requirements for initial and ongoing use.
- Self-selection Decision: The majority of evaluators in both studies said they were not eligible to buy the product or that they would need to talk to a doctor first. In the great majority of these cases, the decision to not try the product right away was the correct one. In addition, very few participants in either study made a serious selection error.

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

7825351

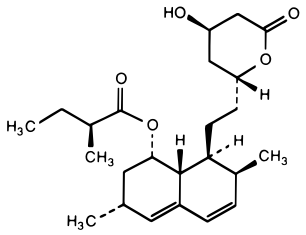
TABLETS

MEVACOR®
(LOVASTATIN)

DESCRIPTION

MEVACOR* (Lovastatin) is a cholesterol lowering agent isolated from a strain of *Aspergillus terreus.* After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is a principal metabolite and 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.

Lovastatin is [1*S*-[1α(*R**),3α,7β,8β(2*S**,4*S**), 8aβ]]-1,2,3,7, 8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. The empirical formula of lovastatin is $C_{24}H_{36}O_5$ and its molecular weight is 404.55. Its structural formula is:



Lovastatin is a white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetonitrile.

Tablets MEVACOR are supplied as 10 mg, 20 mg and 40 mg tablets for oral administration. In addition to the active ingredient lovastatin, each tablet contains the following inactive ingredients: cellulose, lactose, magnesium stearate, and starch. Butylated hydroxyanisole (BHA) is added as a preservative. Tablets MEVACOR 10 mg also contain red ferric oxide and yellow ferric oxide. Tablets MEVACOR 20 mg also contain FD&C Blue 2. Tablets MEVACOR 40 mg also contain D&C Yellow 10 and FD&C Blue 2.

CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological and clinical studies have established that high LDL-C and low high-density lipoprotein cholesterol (HDL-C) are both associated with coronary heart disease. However, the risk of developing coronary heart disease is continuous and graded over the range of cholesterol levels and many coronary events do occur in patients with total cholesterol (total-C) and LDL-C in the lower end of this range.

MEVACOR has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very low-density lipoprotein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of MEVACOR may involve both reduction of VLDL-C concentration, and induction of the LDL receptor, leading to reduced production and*/*or increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with MEVACOR. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that MEVACOR does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, MEVACOR can produce increases of variable magnitude in HDL-C, and modestly reduces VLDL-C and plasma triglycerides (TG) (see Tables I-III under *Clinical Studies*). The effects of MEVACOR on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown.

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* Registered trademark of MERCK & CO., Inc.

MEVACOR is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol.

Pharmacokinetics

Lovastatin is a lactone which 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 lovastatin.

Following an oral dose of ^{14}C-labeled lovastatin in man, 10% of the dose was excreted in urine and 83% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (lovastatin plus ^{14}C-metabolites) peaked at 2 hours and declined rapidly to about 10% of peak by 24 hours postdose. Absorption of lovastatin, estimated relative to an intravenous reference dose, in each of four animal species tested, averaged about 30% of an oral dose. In animal studies, after oral dosing, lovastatin had high selectivity for the liver, where it achieved substantially higher concentrations than in non-target tissues. Lovastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of lovastatin, the availability of drug to the general circulation is low and variable. In a single dose study in four hypercholesterolemic patients, it was estimated that less than 5% of an oral dose of lovastatin reaches the general circulation as active inhibitors. Following administration of lovastatin tablets the coefficient of variation, based on between-subject variability, was approximately 40% for the area under the curve (AUC) of total inhibitory activity in the general circulation.

Both lovastatin and its β-hydroxyacid metabolite are highly bound (>95%) to human plasma proteins. Animal studies demonstrated that lovastatin crosses the blood-brain and placental barriers.

The major active metabolites present in human plasma are the β-hydroxyacid of lovastatin, its 6′-hydroxy derivative, and two additional metabolites. Peak plasma concentrations of both active and total inhibitors were attained within 2 to 4 hours of dose administration. While the recommended therapeutic dose range is 10 to 80 mg/day, linearity of inhibitory activity in the general circulation was established by a single dose study employing lovastatin tablet dosages from 60 to as high as 120 mg. With a once-a-day dosing regimen, plasma concentrations of total inhibitors over a dosing interval achieved a steady state between the second and third days of therapy and were about 1.5 times those following a single dose. When lovastatin was given under fasting conditions, plasma concentrations of total inhibitors were on average about two-thirds those found when lovastatin was administered immediately after a standard test meal.

In a study of patients with severe renal insufficiency (creatinine clearance 10-30 mL/min), the plasma concentrations of total inhibitors after a single dose of lovastatin were approximately two-fold higher than those in healthy volunteers.

In a study including 16 elderly patients between 70-78 years of age who received MEVACOR 80 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 (see PRECAUTIONS, *Geriatric Use*).

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

Lovastatin is a substrate for cytochrome P450 isoform 3A4 (CYP3A4) (see PRECAUTIONS, *Drug Interactions*). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study[**], 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with and 30 and 90 minutes following a single dose of 80 mg lovastatin on the third day. This regimen of grapefruit juice resulted in a mean increase in the serum concentration of lovastatin and its β-hydroxyacid metabolite (as measured by the area under the concentration-time curve) of 15-fold and 5-fold, respectively [as measured using a chemical assay — high performance liquid chromatography]. In a second study, 15 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 40 mg lovastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in

[**] Kantola, T, et al., Clin Pharmacol Ther 1998; 63(4):397-402.

the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using an enzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.34-fold and 1.36-fold, respectively, and of lovastatin and its β-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry — different from that used in the first** study] of 1.94-fold and 1.57-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied.

Clinical Studies in Adults

MEVACOR has been shown to be highly effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of primary hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response was maintained during continuation of therapy. Single daily doses given in the evening were more effective than the same dose given in the morning, perhaps because cholesterol is synthesized mainly at night.

In multicenter, double-blind studies in patients with familial or non-familial hypercholesterolemia, MEVACOR, administered in doses ranging from 10 mg q.p.m. to 40 mg b.i.d., was compared to placebo. MEVACOR consistently and significantly decreased plasma total-C, LDL-C, total-C/HDL-C ratio and LDL-C/HDL-C ratio. In addition, MEVACOR produced increases of variable magnitude in HDL-C, and modestly decreased VLDL-C and plasma TG (see Tables I through III for dose response results).

The results of a study in patients with primary hypercholesterolemia are presented in Table I.

TABLE I
MEVACOR vs. Placebo
(Mean Percent Change from Baseline After 6 Weeks)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C	TG.
Placebo	33	–2	–1	–1	0	+1	+9
MEVACOR							
10 mg q.p.m.	33	–16	–21	+5	–24	–19	–10
20 mg q.p.m.	33	–19	–27	+6	–30	–23	+9
10 mg b.i.d.	32	–19	–28	+8	–33	–25	–7
40 mg q.p.m.	33	–22	–31	+5	–33	–25	–8
20 mg b.i.d.	36	–24	–32	+2	–32	–24	–6

MEVACOR was compared to cholestyramine in a randomized open parallel study. The study was performed with patients with hypercholesterolemia who were at high risk of myocardial infarction. Summary results are presented in Table II.

TABLE II
MEVACOR vs. Cholestyramine
(Percent Change from Baseline After 12 Weeks)

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TG. (mean)
MEVACOR								
20 mg b.i.d.	85	–27	–32	+9	–36	–31	–34	–21
40 mg b.i.d.	88	–34	–42	+8	–44	–37	–31	–27
Cholestyramine								
12 g b.i.d.	88	–17	–23	+8	–27	–21	+2	+11

MEVACOR was studied in controlled trials in hypercholesterolemic patients with well-controlled non-insulin dependent diabetes mellitus with normal renal function. The effect of MEVACOR on lipids and lipoproteins and the safety profile of MEVACOR were similar to that demonstrated in studies in nondiabetics. MEVACOR had no clinically important effect on glycemic control or on the dose requirement of oral hypoglycemic agents.

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240-300 mg/dL [6.2 mmol/L - 7.6 mmol/L], LDL-C >160 mg/dL [4.1 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. All changes in the lipid measurements (Table III) in MEVACOR treated patients were dose-related and significantly different from placebo ($p \leq 0.001$). These results were sustained throughout the study.

TABLE III
MEVACOR vs. Placebo
(Percent Change from Baseline —
Average Values Between Weeks 12 and 48)

DOSAGE	N**	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	TG. (median)
Placebo	1663	+0.7	+0.4	+2.0	+0.2	+0.6	+4
MEVACOR							
20 mg q.p.m.	1642	–17	–24	+6.6	–27	–21	–10
40 mg q.p.m.	1645	–22	–30	+7.2	–34	–26	–14
20 mg b.i.d.	1646	–24	–34	+8.6	–38	–29	–16
40 mg b.i.d.	1649	–29	–40	+9.5	–44	–34	–19

**Patients enrolled

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

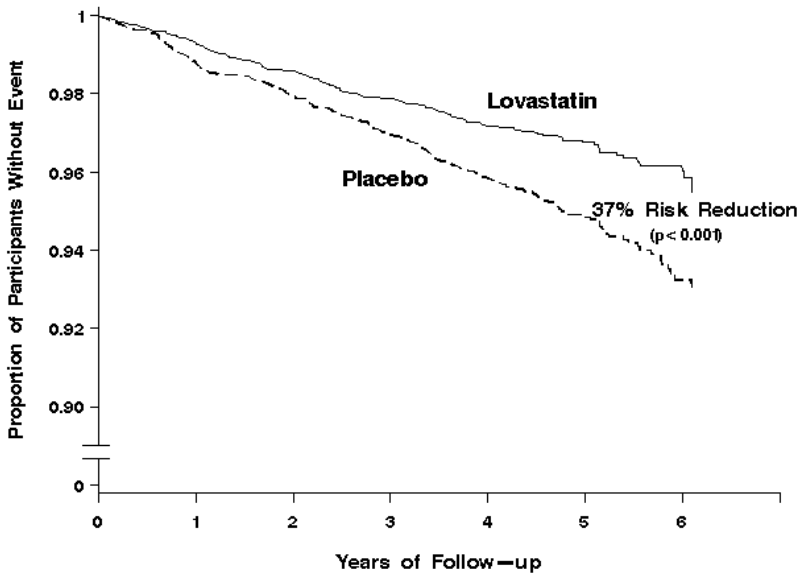
The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a double-blind, randomized, placebo-controlled, primary prevention study, demonstrated that treatment with MEVACOR decreased the rate of acute major coronary events (composite endpoint of myocardial infarction, unstable angina, and sudden cardiac death) compared with placebo during a median of 5.1 years of follow-up. Participants were middle-aged and elderly men (ages 45-73) and women (ages 55-73) without symptomatic cardiovascular disease with average to moderately elevated total-C and LDL-C, below average HDL-C, and who were at high risk based on elevated total-C/HDL-C. In addition to age, 63% of the participants had at least one other risk factor (baseline HDL-C <35 mg/dL, hypertension, family history, smoking and diabetes).

AFCAPS/TexCAPS enrolled 6,605 participants (5,608 men, 997 women) based on the following lipid entry criteria: total-C range of 180-264 mg/dL, LDL-C range of 130-190 mg/dL, HDL-C of ≤45 mg/dL for men and ≤47 mg/dL for women, and TG of ≤400 mg/dL. Participants were treated with standard care, including diet, and either MEVACOR 20-40 mg daily (n= 3,304) or placebo (n= 3,301). Approximately 50% of the participants treated with MEVACOR were titrated to 40 mg daily when their LDL-C remained >110 mg/dL at the 20-mg starting dose.

MEVACOR reduced the risk of a first acute major coronary event, the primary efficacy endpoint, by 37% (MEVACOR 3.5%, placebo 5.5%; p<0.001; Figure 1). A first acute major coronary event was defined as myocardial infarction (54 participants on MEVACOR, 94 on placebo) or unstable angina (54 vs. 80) or sudden cardiac death (8 vs. 9). Furthermore, among the secondary endpoints, MEVACOR reduced the risk of unstable angina by 32% (1.8 vs. 2.6%; p=0.023), of myocardial infarction by 40% (1.7 vs. 2.9%; p=0.002), and of undergoing coronary revascularization procedures (e.g., coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 33% (3.2 vs. 4.8%; p=0.001). Trends in risk reduction associated with treatment with MEVACOR were consistent across men and women, smokers and non-smokers, hypertensives and non-hypertensives, and older and younger participants. Participants with ≥2 risk factors had risk reductions (RR) in both acute major coronary events (RR 43%) and coronary revascularization procedures (RR 37%). Because there were too few events among those participants with age as their only risk factor in this study, the effect of MEVACOR on outcomes could not be adequately assessed in this subgroup.

Figure 1

Acute Major Coronary Events
(Primary Endpoint)



Atherosclerosis

In the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT), the effect of therapy with lovastatin on coronary atherosclerosis was assessed by coronary angiography in hyperlipidemic patients. In the randomized, double-blind, controlled clinical trial, patients were treated with conventional measures (usually diet and 325 mg of aspirin every other day) and either lovastatin 20-80 mg daily or placebo. Angiograms were evaluated at baseline and at two years by computerized quantitative coronary angiography (QCA). Lovastatin significantly slowed the progression of lesions as measured by the mean change per-patient in minimum lumen diameter (the primary endpoint) and percent diameter stenosis, and decreased the proportions of patients categorized with disease progression (33% vs. 50%) and with new lesions (16% vs. 32%).

In a similarly designed trial, the Monitored Atherosclerosis Regression Study (MARS), patients were treated with diet and either lovastatin 80 mg daily or placebo. No statistically significant difference between lovastatin and placebo was seen for the primary endpoint (mean change per patient in percent diameter stenosis of all lesions), or for most secondary QCA endpoints. Visual assessment by angiographers who formed a consensus opinion of overall angiographic change (Global Change Score) was also a secondary endpoint. By this endpoint, significant slowing of disease was seen, with regression in 23% of patients treated with lovastatin compared to 11% of placebo patients.

In the Familial Atherosclerosis Treatment Study (FATS), either lovastatin or niacin in combination with a bile acid sequestrant for 2.5 years in hyperlipidemic subjects significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions by QCA compared to diet and, in some cases, low-dose resin.

The effect of lovastatin on the progression of atherosclerosis in the coronary arteries has been corroborated by similar findings in another vasculature. In the Asymptomatic Carotid Artery Progression Study (ACAPS), the effect of therapy with lovastatin on carotid atherosclerosis was assessed by B-mode ultrasonography in hyperlipidemic patients with early carotid lesions and without known coronary heart disease at baseline. In this double-blind, controlled clinical trial, 919 patients were randomized in a 2 x 2 factorial design to placebo, lovastatin 10-40 mg daily and/or warfarin. Ultrasonograms of the carotid walls were used to determine the change per patient from baseline to three years in mean maximum intimal-medial thickness (IMT) of 12 measured segments. There was a significant regression of carotid lesions in patients receiving lovastatin alone compared to those receiving placebo alone (p=0.001). The predictive value of changes in IMT for stroke has not yet been established. In the lovastatin group there was a

significant reduction in the number of patients with major cardiovascular events relative to the placebo group (5 vs. 14) and a significant reduction in all-cause mortality (1 vs. 8).

Eye

There was a high prevalence of baseline lenticular opacities in the patient population included in the early clinical trials with lovastatin. During these trials the appearance of new opacities was noted in both the lovastatin and placebo groups. There was no clinically significant change in visual acuity in the patients who had new opacities reported nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity.

A three-year, double-blind, placebo-controlled study in hypercholesterolemic patients to assess the effect of lovastatin on the human lens demonstrated that there were no clinically or statistically significant differences between the lovastatin and placebo groups in the incidence, type or progression of lenticular opacities. There are no controlled clinical data assessing the lens available for treatment beyond three years.

Clinical Studies in Adolescent Patients

Efficacy of Lovastatin in Adolescent Boys with Heterozygous Familial Hypercholesterolemia

In a double-blind, placebo-controlled study, 132 boys 10-17 years of age (mean age 12.7 yrs) with heterozygous familial hypercholesterolemia (heFH) were randomized to lovastatin (n=67) or placebo (n=65) for 48 weeks. Inclusion in the study required a baseline LDL-C level between 189 and 500 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The mean baseline LDL-C value was 253.1 mg/dL (range: 171-379 mg/dL) in the MEVACOR group compared to 248.2 mg/dL (range: 158.5-413.5 mg/dL) in the placebo group. The dosage of lovastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter.

MEVACOR significantly decreased plasma levels of total-C, LDL-C and apolipoprotein B (see Table IV).

TABLE IV
Lipid-lowering Effects of Lovastatin in Adolescent Boys with Heterozygous Familial Hypercholesterolemia
(Mean Percent Change from Baseline at week 48 in Intention-to-Treat Population)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	TG.*	Apolipoprotein B
Placebo	61	-1.1	-1.4	-2.2	-1.4	-4.4
MEVACOR	64	-19.3	-24.2	+1.1	-1.9	-21

*data presented as median percent changes

The mean achieved LDL-C value was 190.9 mg/dL (range: 108-336 mg/dL) in the MEVACOR group compared to 244.8 mg/dL (range: 135-404 mg/dL) in the placebo group.

Efficacy of Lovastatin in Post-menarchal Girls with Heterozygous Familial Hypercholesterolemia

In a double-blind, placebo-controlled study, 54 girls 10-17 years of age who were at least 1 year post-menarche with heFH were randomized to lovastatin (n=35) or placebo (n=19) for 24 weeks. Inclusion in the study required a baseline LDL-C level of 160-400 mg/dL and a parental history of familial hypercholesterolemia. The mean baseline LDL-C value was 218.3 mg/dL (range: 136.3-363.7 mg/dL) in the MEVACOR group compared to 198.8 mg/dL (range: 151.1-283.1 mg/dL) in the placebo group. The dosage of lovastatin (once daily in the evening) was 20 mg for the first 4 weeks, and 40 mg thereafter.

MEVACOR significantly decreased plasma levels of total-C, LDL-C, and apolipoprotein B (see Table V).

TABLE V
Lipid-lowering Effects of Lovastatin in Post-menarchal Girls with Heterozygous Familial Hypercholesterolemia
(Mean Percent Change from Baseline at Week 24 in Intention-to-Treat Population)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	TG.*	Apolipoprotein B
Placebo	18	+3.6	+2.5	+4.8	-3.0	+6.4
MEVACOR	35	-22.4	-29.2	+2.4	-22.7	-24.4

*data presented as median percent changes

The mean achieved LDL-C value was 154.5 mg/dL (range: 82-286 mg/dL) in the MEVACOR group compared to 203.5 mg/dL (range: 135-304 mg/dL) in the placebo group.

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

INDICATIONS AND USAGE

Therapy with MEVACOR should be a component of multiple risk factor intervention in those individuals with dyslipidemia at risk for atherosclerotic vascular disease. MEVACOR should be used in addition to a diet restricted in saturated fat and cholesterol as part of a treatment strategy to lower total-C and LDL-C to target levels when the response to diet and other nonpharmacological measures alone has been inadequate to reduce risk.

Primary Prevention of Coronary Heart Disease

In individuals without symptomatic cardiovascular disease, average to moderately elevated total-C and LDL-C, and below average HDL-C, MEVACOR is indicated to reduce the risk of:

- Myocardial infarction
- Unstable angina
- Coronary revascularization procedures

(See CLINICAL PHARMACOLOGY, *Clinical Studies*.)

Coronary Heart Disease

MEVACOR is indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total-C and LDL-C to target levels.

Hypercholesterolemia

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. MEVACOR is indicated as an adjunct to diet for the reduction of elevated total-C and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb[***]), when the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.

Adolescent Patients with Heterozygous Familial Hypercholesterolemia

MEVACOR is indicated as an adjunct to diet to reduce total-C, LDL-C and apolipoprotein 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-C remains >189 mg/dL or
2. LDL-C remains >160 mg/dL and:
   - there is a positive family history of premature cardiovascular disease or
   - two or more other CVD risk factors are present in the adolescent patient

General Recommendations

Prior to initiating therapy with lovastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total-C, HDL-C, and TG. For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

$$\text{LDL-C} = \text{total-C} - [0.2 \times (\text{TG}) + \text{HDL-C}]$$

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, MEVACOR is not indicated.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

[***] Classification of Hyperlipoproteinemias

		Lipid Elevations	
Type	Lipoproteins elevated	major	minor
I	chylomicrons	TG	↑→C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	↑→C
V (rare)	chylomicrons, VLDL	TG	↑→C

IDL = intermediate-density lipoprotein.

NCEP Treatment Guidelines:
LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes
and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2+ Risk factors (10 year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥ 160
0-1 Risk factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

† CHD, coronary heart disease
†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
††† Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dL (see NCEP Guidelines above).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy.

Although MEVACOR may be useful to reduce elevated LDL-C levels in patients with combined hypercholesterolemia and hypertriglyceridemia where hypercholesterolemia is the major abnormality (Type IIb hyperlipoproteinemia), it has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL or IDL (i.e., hyperlipoproteinemia types I, III, IV, or V).***

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

Children treated with lovastatin in adolescence should be re-evaluated in adulthood and appropriate changes made to their cholesterol-lowering regimen to achieve adult goals for LDL-C.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. 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. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR is contraindicated during pregnancy and in nursing mothers. **MEVACOR 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, MEVACOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, *Pregnancy*).

WARNINGS

Myopathy/Rhabdomyolysis

Lovastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

- **The risk of myopathy/rhabdomyolysis is increased by concomitant use of lovastatin with the following:**

  Potent inhibitors of CYP3A4: Cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily), particularly with higher doses of lovastatin (see below; CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, CYP3A4 Interactions*).

  Lipid-lowering drugs that can cause myopathy when given alone: Gemfibrozil, other fibrates, or lipid-lowering doses (≥1 g/day) of niacin, particularly with higher doses of lovastatin (see below; CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone*).

  Other drugs: The risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class (see PRECAUTIONS, *Drug Interactions, Other drug interactions*).

- **The risk of myopathy/rhabdomyolysis is dose related.** In a clinical study (EXCEL) in which patients were carefully monitored and some interacting drugs were excluded, there was one case of myopathy among 4933 patients randomized to lovastatin 20-40 mg daily for 48 weeks, and 4 among 1649 patients randomized to 80 mg daily.

CONSEQUENTLY:

1. Use of lovastatin concomitantly with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided. If treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is unavoidable, therapy with lovastatin should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

2. The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with cyclosporine, gemfibrozil, other fibrates or lipid-lowering doses (≥1 g/day) of niacin. The combined use of lovastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Addition of these drugs to lovastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained.

3. The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of lovastatin at doses higher than 40 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy.

4. All patients starting therapy with lovastatin, or whose dose of lovastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Lovastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and/or a CK level >10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with lovastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

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

Liver Dysfunction

Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin, and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), the incidence of persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

In AFCAPS/TexCAPS, the number of participants with consecutive elevations of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 times the upper limit of normal), over a median of 5.1 years of follow-up, was not significantly different between the MEVACOR and placebo groups (18 [0.6%] vs. 11 [0.3%]). The starting dose of MEVACOR was 20 mg/day; 50% of the MEVACOR treated participants were titrated to 40 mg/day at Week 18. Of the 18 participants on MEVACOR with consecutive elevations of either ALT or AST, 11 (0.7%) elevations occurred in participants taking 20 mg/day, while 7 (0.4%) elevations occurred in participants titrated to 40 mg/day. Elevated transaminases resulted in discontinuation of 6 (0.2%) participants from therapy in the MEVACOR group (n=3,304) and 4 (0.1%) in the placebo group (n=3,301).

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter (e.g., semiannually). 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) returns to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of therapy with MEVACOR is recommended.

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 disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

PRECAUTIONS

General

Lovastatin may elevate creatine phosphokinase and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia

MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Information for Patients

Patients should be advised about substances they should not take concomitantly with lovastatin and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see list below and WARNINGS, *Myopathy/Rhabdomyolysis*). Patients should also be advised to inform other physicians prescribing a new medication that they are taking MEVACOR.

Drug Interactions

CYP3A4 Interactions

Lovastatin 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. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of lovastatin.

See WARNINGS, *Myopathy/Rhabdomyolysis*, and CLINICAL PHARMACOLOGY, *Pharmacokinetics.*

Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
HIV protease inhibitors
Nefazodone
Cyclosporine
Large quantities of grapefruit juice (>1 quart daily)

Interactions with lipid-lowering drugs that can cause myopathy when given alone

The risk of myopathy is also increased by the following lipid-lowering drugs that are not potent CYP3A4 inhibitors, but which can cause myopathy when given alone.

See WARNINGS, *Myopathy/Rhabdomyolysis.*
Gemfibrozil
Other fibrates
Niacin (nicotinic acid) (≥1 g/day)

Other drug interactions

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with a closely related member of the HMG-CoA reductase inhibitor class (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than two-second increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure 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 lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Oral Hypoglycemic Agents: In pharmacokinetic studies of MEVACOR in hypercholesterolemic non-insulin dependent diabetic patients, there was no drug interaction with glipizide or with chlorpropamide (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of

endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity

Lovastatin 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 drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level (C_{max}) 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 lovastatin at a dose of 180 mg/kg/day, a dose which produced plasma drug levels (C_{max}) which were about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Cataracts were seen in dogs treated for 11 and 28 weeks at 180 mg/kg/day and 1 year at 60 mg/kg/day.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on a mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of MEVACOR.)

There was an increase in incidence of papilloma in the non-glandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males at drug exposures between 2-7 times that of human exposure at 80 mg/day (doses in rats were 5, 30 and 180 mg/kg/day).

An increased incidence of thyroid neoplasms in rats appears to be a response that has been seen with other HMG-CoA reductase inhibitors.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high dose females and mid- and high dose males, with a maximum incidence of 90 percent 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 mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* 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 or mouse 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.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration

(necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established.

Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m^2 surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose).

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[†] of approximately 100 prospectively followed pregnancies in women exposed to MEVACOR or another structurally related HMG-CoA reductase inhibitor, 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. As safety in pregnant women has not been established and there is no apparent benefit to therapy with MEVACOR during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. MEVACOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Nursing Mothers

It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking MEVACOR should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness in patients 10-17 years of age with heFH have been evaluated in controlled clinical trials of 48 weeks duration in adolescent boys and controlled clinical trials of 24 weeks duration in girls who were at least 1 year post-menarche. Patients treated with lovastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population**. In these limited controlled studies, there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls. See CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescent Patients*; ADVERSE REACTIONS, *Adolescent Patients*; and DOSAGE AND ADMINISTRATION, *Adolescent Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolemia*. Adolescent females should be counseled on appropriate contraceptive methods while on lovastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy*). **Lovastatin has not been studied in pre-pubertal patients or patients younger than 10 years of age.**

Geriatric Use

A pharmacokinetic study with lovastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age; however, clinical study experience in the elderly indicates that dosage adjustment based on this age-related pharmacokinetic difference is not needed. In the two large clinical studies conducted with lovastatin (EXCEL and AFCAPS/TexCAPS), 21% (3094/14850) of patients were ≥65 years of age. Lipid-lowering efficacy with lovastatin was at least as great in elderly patients compared with younger patients, and there were no overall differences in safety over the 20 to 80 mg/day dosage range (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

MEVACOR is generally well tolerated; adverse reactions usually have been mild and transient.

[†] 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.

Phase III Clinical Studies

In Phase III controlled clinical studies involving 613 patients treated with MEVACOR, the adverse experience profile was similar to that shown below for the 8,245-patient EXCEL study (see *Expanded Clinical Evaluation of Lovastatin [EXCEL] Study*).

Persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 11% of patients had elevations of CK levels of at least twice the normal value on one or more occasions. The corresponding values for the control agent cholestyramine was 9 percent. This was attributable to the noncardiac fraction of CK. Large increases in CK have sometimes been reported (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240-300 mg/dL [6.2-7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably or definitely drug-related in ≥1% in any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

	Placebo (N = 1663) %	MEVACOR 20 mg q.p.m. (N = 1642) %	MEVACOR 40 mg q.p.m. (N = 1645) %	MEVACOR 20 mg b.i.d. (N = 1646) %	MEVACOR 40 mg b.i.d. (N = 1649) %
Body As a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse experiences reported as possibly, probably or definitely drug-related in 0.5 to 1.0 percent of patients in any drug-treated group are listed below. In all these cases the incidence on drug and placebo was not statistically different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation, dry mouth, vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthralgia; *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus; *Special Senses:* eye irritation.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences which were rated by the investigator as possibly, probably or definitely related to therapy with MEVACOR. The value for the placebo group was 2.5%.

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

In AFCAPS/TexCAPS (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 6,605 participants treated with 20-40 mg/day of MEVACOR (n=3,304) or placebo (n=3,301), the safety and tolerability profile of the group treated with MEVACOR was comparable to that of the group treated with placebo during a median of 5.1 years of follow-up. The adverse experiences reported in AFCAPS/TexCAPS were similar to those reported in EXCEL (see ADVERSE REACTIONS, *Expanded Clinical Evaluation of Lovastatin (EXCEL) Study*).

Concomitant Therapy

In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggests that the addition of gemfibrozil to therapy with lovastatin is not associated with greater

reduction in LDL-C than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with cyclosporine, gemfibrozil or niacin (nicotinic acid). The combined use of lovastatin at doses exceeding 20 mg/day with cyclosporine, gemfibrozil, other fibrates or lipid-lowering doses (≥1 g/day) of niacin should be avoided (see WARNINGS, *Myopathy/Rhabdomyolysis*).

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with lovastatin therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-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.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Adolescent Patients (ages 10-17 years)

In a 48-week controlled study in adolescent boys with heFH (n=132) and a 24-week controlled study in girls who were at least 1 year post-menarche with heFH (n=54), the safety and tolerability profile of the groups treated with MEVACOR (10 to 40 mg daily) was generally similar to that of the groups treated with placebo (see CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescent Patients* and PRECAUTIONS, *Pediatric Use*).

OVERDOSAGE

After oral administration of MEVACOR to mice, the median lethal dose observed was >15 g/m^2.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5-6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

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

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR (see NCEP Treatment Guidelines for details on dietary therapy). MEVACOR should be given with meals.

Adult Patients

The usual recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 10-80 mg/day in single or two divided doses; the maximum recommended dose is 80 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Guidelines and CLINICAL PHARMACOLOGY). Patients requiring reductions in LDL-C of 20% or more to achieve their goal (see INDICATIONS AND USAGE) should be started on 20 mg/day of MEVACOR. A starting dose of 10 mg may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall significantly below the targeted range.

Dosage in Patients taking Cyclosporine

In patients taking cyclosporine concomitantly with lovastatin (see WARNINGS, *Myopathy/Rhabdomyolysis*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.

Dosage in Patients taking Amiodarone or Verapamil

In patients taking amiodarone or verapamil concomitantly with MEVACOR, the dose should not exceed 40 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*, *Other drug interactions*).

Adolescent Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolemia

The recommended dosing range is 10-40 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 Guidelines[††], CLINICAL PHARMACOLOGY, and INDICATIONS AND USAGE). Patients requiring reductions in LDL-C of 20% or more to achieve their goal should be started on 20 mg/day of MEVACOR. A starting dose of 10 mg may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more.

Concomitant Lipid-Lowering Therapy

MEVACOR is effective alone or when used concomitantly with bile-acid sequestrants. If MEVACOR is used in combination with gemfibrozil, other fibrates or lipid-lowering doses (≥ 1g/day) of niacin, the dose of MEVACOR should not exceed 20 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

Dosage in Patients with Renal Insufficiency

In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY and WARNINGS, *Myopathy/Rhabdomyolysis*).

HOW SUPPLIED

No. 3560 — Tablets MEVACOR 10 mg are peach, octagonal tablets, coded MSD 730 on one side and MEVACOR on the other. They are supplied as follows:

NDC 0006-0730-61 unit of use bottles of 60.

No. 3561 — Tablets MEVACOR 20 mg are light blue, octagonal tablets, coded MSD 731 on one side and MEVACOR on the other. They are supplied as follows:

NDC 0006-0731-61 unit of use bottles of 60
NDC 0006-0731-94 unit of use bottles of 90
NDC 0006-0731-28 unit dose packages of 100
NDC 0006-0731-82 bottles of 1,000
NDC 0006-0731-87 bottles of 10,000.

No. 3562 — Tablets MEVACOR 40 mg are green, octagonal tablets, coded MSD 732 on one side and MEVACOR on the other. They are supplied as follows:

NDC 0006-0732-61 unit of use bottles of 60
NDC 0006-0732-94 unit of use bottles of 90
NDC 0006-0732-82 bottles of 1,000
NDC 0006-0732-87 bottles of 10,000.

Storage

Store between 5-30°C (41-86°F). Tablets MEVACOR must be protected from light and stored in a well-closed, light-resistant container.

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued June 2002

[††] 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.

Once-a-day
MEVACOR™ OTC
Lovastatin 20 mg
CHOLESTEROL REDUCER

PULL TAB TO OPEN

DO NOT USE IF CARTON IS OPEN OR PRINTED FOIL SEAL UNDER BOTTLE CAP IS OPEN OR TORN.

Keep this carton and contents, they contain important information.

Once-a-day MEVACOR™ OTC

Lovastatin 20 mg
CHOLESTEROL REDUCER

- For people with elevated LDL "bad" cholesterol between 130–170 mg/dL
- To reduce LDL cholesterol to 129 or below and keep it down

45 TABLETS

Read back for more information

Once-a-day
MEVACOR™ OTC
Lovastatin 20 mg
CHOLESTEROL REDUCER

PULL TAB TO OPEN

DO NOT USE IF CARTON IS OPEN OR PRINTED FOIL SEAL UNDER BOTTLE CAP IS OPEN OR TORN.

Keep this carton and contents, they contain important information.

Read the warnings and directions before use.
Store at 5°-30° C (41°- 86° F).

LOT NO. XX-XXXX
EXP. XXXXXXXXX

Distributed by:
Johnson & Johnson • Merck
CONSUMER PHARMACEUTICALS CO.
FORT WASHINGTON, PA 19034 USA

Drug Facts

Active ingredient (in each tablet) — ***Purpose***

Lovastatin 20 mg ..... Cholesterol reducer

Use To help lower LDL "bad" cholesterol, which may prevent a first heart attack. This product is for people who meet the requirements in the sections below.

Warnings

Do not use if

- **Liver disease:** Do NOT use if you have liver disease.
- Do NOT use if you have had any muscle pain, weakness or tenderness from taking a cholesterol-lowering medicine.
- **Pregnant or breast-feeding:** Do NOT use if you are pregnant or breast-feeding.
- **Allergic to lovastatin:** Do NOT use if you know you are allergic to lovastatin or the inactive ingredients in this medicine, as listed below.

Ask your doctor or pharmacist before use if you are taking

- Any prescription medicine: If you are taking any prescription medicine, ask your doctor or pharmacist before taking MEVACOR™ OTC. Certain drugs can interact with MEVACOR™ OTC and can increase the possibility of side effects.
- Other cholesterol-lowering medicine: Do NOT substitute MEVACOR™ OTC for your prescription or non-prescription cholesterol-lowering medicine without talking to your doctor.
- New prescriptions: Tell your doctor or pharmacist you are taking MEVACOR™ OTC before you begin taking any new prescription medicine.

Do NOT use unless directed by your doctor if you have

- very high LDL "bad" cholesterol 171-400 mg/dL
- high triglycerides 200-900 mg/dL
- healthy HDL "good" cholesterol 60-200 mg/dL
- had a stroke
- ever had heart disease (heart attack or angina)
- diabetes

Stop use and ask your doctor if you develop any unexplained muscle pain, weakness or tenderness. Stop use immediately. This can be a sign of a rare but serious side effect.

If you are diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

How to decide if MEVACOR™ OTC is right for you

Before using you must have

- Tried a healthy diet and exercise to reduce your cholesterol.
- Had a fasting cholesterol test within the last year. If you do not know your numbers, call your doctor to get them or get a new test.

Who can use: You must have YES (blue) answers to all 4 of the following. Total cholesterol is important, but you must know your exact fasting LDL and HDL numbers.

1 MEVACOR™ OTC is **only** for men 45 years or older **AND** women 55 years or older

Yes, I am a man 45 or older or a woman 55 or older – continue ▶

Men 44 or younger or women 54 or younger
STOP **Do not use - ask your doctor or pharmacist.**

2 MEVACOR™ OTC is **only** for people with LDL "bad" cholesterol between **130 – 170 mg/dL**

Yes, my LDL before use is 130-170 mg/dL – continue ▶

Between 1-129 mg/dL or 171-400 mg/dL or don't know
STOP **Do not use - ask your doctor or pharmacist.**

3 MEVACOR™ OTC is only for people with one or more of these conditions that increase heart risk:
(If yes to any, you may need MEVACOR™ OTC.)

- ▶ You are a smoker **(may need MEVACOR™ OTC)** **OR**
- ▶ HDL "good" cholesterol 1-39 mg/dL **(too low)** **OR**
- ▶ Heart attack or angina in father or brother before 55; mother or sister before 65 **OR**
- ▶ High blood pressure

Yes, I have one or more of the above – continue ▶

I have none of the above or I'm not sure/don't know
STOP **Do not use - ask your doctor or pharmacist.**

4 MEVACOR™ OTC is only for people who are free of **ALL** conditions in the ***Warnings*** section above

Yes, I am free of all *Warnings* above – continue ▶

I have a condition listed in ***Warnings*** section or don't know
STOP **Do not use - ask your doctor or pharmacist.**

I have all YES (blue) answers. I can use MEVACOR™ OTC see directions below.

I have a STOP answer I cannot use.

Directions

1 Take one tablet daily:

- If you stop taking MEVACOR™ OTC, your cholesterol will go back up.
- For best results, take it with the evening meal. (Your body makes more cholesterol at night.)
- Continue to eat a healthy diet and exercise.
- Do not take more than one tablet per day.

2 Test at 6 weeks: See if your LDL test result is 1-129 mg/dL: "YES" or "NO"?

- **NO –** If at 6 weeks your LDL "bad" cholesterol is higher than 129 mg/dL, STOP stop taking MEVACOR™ OTC. Talk to your doctor. MEVACOR™ OTC may not be enough for you.
- **YES –** If at 6 weeks your LDL "bad" cholesterol is 1-129 mg/dL, it's working, keep taking it daily and test your cholesterol once a year. If you stop, your cholesterol will go back up.
- For information on cholesterol testing, talk to your pharmacist or doctor.

3 Talk to your doctor if there is a change in your health:

- New prescriptions: Tell your doctor you are taking MEVACOR™ OTC before you begin taking any new prescription medicine.
- New medical condition: If diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.
- Unexplained muscle pain: Stop use immediately and talk to your doctor if you develop any unexplained muscle pain, weakness or tenderness. This can be a sign of a rare but serious side effect. ▼

Drug Facts (continued)

Inactive ingredients Butylated hydroxyanisole (BHA), cellulose, FD&C blue No. 2 aluminum lake, lactose, magnesium stearate, and starch.

Other information See inside package for additional information or call toll free 1-800-XXX-XXXX or visit us on the web at www.xxxxxxx.com

IMPORTANT INFORMATION ABOUT MEVACOR™ OTC (Lovastatin 20 mg). PLEASE READ THIS PACKAGE INSERT AND SAVE FOR FUTURE USE.

Once-a-day MEVACOR™ Lovastatin 20 mg CHOLESTEROL REDUCER OTC

What is MEVACOR™ OTC?

MEVACOR™ OTC contains an ingredient that has been used for over 15 years by millions of people to lower their cholesterol. MEVACOR™ OTC should be used to help lower your LDL cholesterol as part of a total heart healthy program, including eating a low-fat, low-cholesterol diet and exercising. This program may reduce your risk of suffering a first heart attack or stroke.

What is cholesterol and why can it be a problem?

Cholesterol is a fat-like substance that is made in your liver, and can be found in food that you eat. Your body needs cholesterol to survive (to build cells, for example), but too much of it can cause problems. It can build up in your arteries and make it harder for your blood to flow. When this happens in the arteries of your heart, it can cause chest pain (angina), or if the artery becomes totally blocked, a heart attack. High cholesterol may be due to many factors and often runs in families. These factors include eating too much food high in saturated fats, hereditary conditions, and certain illnesses such as thyroid or kidney disease.

What are LDL and HDL cholesterol?

Cholesterol comes in two main forms, LDL and HDL. LDL cholesterol can build up in your arteries; this is why it is considered the "bad" cholesterol. HDL is considered "good" cholesterol because it helps remove the "bad" cholesterol from your arteries. An easy way to think of HDL is "H" for Healthy. For good heart health, just remember that LDL levels should be Low and HDL levels should be High. Total cholesterol is made up of LDL and HDL cholesterol, and other blood fats, so people with high total cholesterol tend to have high LDL cholesterol as well.

How does MEVACOR™ OTC work?

MEVACOR™ OTC helps your liver produce less cholesterol. As a result, MEVACOR™ OTC reduces the level of LDL "bad" cholesterol in the blood. Because your body makes cholesterol every day, you need to take MEVACOR™ OTC daily to control it. With continued use, MEVACOR™ OTC can help you keep your cholesterol down, which could lead to a healthier heart.

What are the side effects of MEVACOR™ OTC?

The active ingredient in MEVACOR™ OTC has been generally well tolerated. Side effects have usually been mild. However, as with most drugs, serious side effects may occur. If the following or any other side effects occur while taking MEVACOR™ OTC, stop use and talk to your doctor right away.

- Any unexplained muscle pain, weakness or tenderness not caused by a cold, flu, or recent strain or injury. This can be a sign of a rare but potentially serious side effect. The risk of this side effect may increase if you take medicine that can interact with MEVACOR™ OTC.

Things you can do to have a healthy heart

- **Eat a low-fat, low-cholesterol diet** – Avoiding high-fat foods can help you lower your cholesterol, including your LDL "bad" cholesterol.
- **Exercise** – Exercising three or more times a week may reduce your chances of having heart disease. Talk to your doctor before starting any exercise program.
- **Quit smoking** – Smoking is another problem for your heart. Although smoking does not raise your cholesterol, it increases your risk for heart attack, stroke, and cancer.
- **Lower your blood pressure if it is too high** – High blood pressure increases your risk for heart attack or stroke. Have your blood pressure checked regularly. If blood pressure medicine is prescribed for you, remember to take it.

Before using MEVACOR™ OTC, you should carefully read the back of the package and this package insert to determine if MEVACOR™ OTC is right for you.

Before using, you must have

- Tried a healthy diet and exercise to reduce your cholesterol.
- Had a fasting cholesterol test within the last year. If you do not know your numbers, call your doctor to get them or get a new test.
- If you are not sure if MEVACOR™ OTC is right for you, talk to your doctor or pharmacist or call 1-800-XXX-XXXX to reach a product specialist or visit us on the web at www.xxxxxxx.com.

Warnings

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- Do NOT use if you have had any muscle pain, weakness, or tenderness from taking a cholesterol-lowering medicine.
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- Other cholesterol-lowering medicine: Do NOT substitute MEVACOR™ OTC for your prescription or non-prescription cholesterol-lowering medicine without talking to your doctor.
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- high triglycerides 200-900 mg/dL
- healthy HDL "good" cholesterol 60-200 mg/dL
- ever had heart disease (heart attack or angina)
- had a stroke
- diabetes

Stop use and ask your doctor if you develop any unexplained muscle pain, weakness or tenderness. Stop use immediately. This can be a sign of a rare but serious side effect.

If you are diagnosed with a new medical condition, tell your doctor you are taking MEVACOR™ OTC.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

When using this product

- Do not use MEVACOR™ OTC with the following medicines because they can interact, and serious side effects may occur when they are taken with MEVACOR™ OTC: Itraconazole (SPORANOX®*), Ketoconazole, Erythromycin, Clarithromycin (BIAXIN®*), Protease inhibitors, Nefazodone (SERZONE®*). Ask your doctor before use if you are taking Cyclosporine, Gemfibrozil (LOPID®*), or Niacin (daily doses of 1,000 mg or more), because they may also interact with MEVACOR™ OTC.
- Dietary precaution: People who consume a large quantity of grapefruit juice daily (more than one quart a day) should not use MEVACOR™ OTC.

How to decide if MEVACOR™ OTC is right for you

Before using you must have

- Tried a healthy diet and exercise to reduce your cholesterol.
- Had a fasting cholesterol test within the last year. If you do not know your numbers, call your doctor to get them or get a new test.

Who can use: You must have YES answers to all 4 of the following. Total cholesterol is important, but you must know your exact fasting LDL and HDL numbers.

1. I am a man 45 or older or a woman 55 or older
2. My LDL cholesterol before use is 130-170 mg/dL
3. I have one or more of these conditions that increase heart risk. (If yes to any, you may need MEVACOR™ OTC.)
   - I am a smoker (may need MEVACOR™ OTC) OR
   - HDL "good" cholesterol 1-39 mg/dL (too low) OR
   - Heart attack or angina in father or brother before 55; mother or sister before 65 OR
   - High blood pressure
4. I am free of **ALL** of the conditions in the ***Warnings*** section above.

Directions

- Take one tablet daily.
- If you stop taking MEVACOR™ OTC, your cholesterol will go back up.
- For best results, take it with the evening meal. (Your body makes more cholesterol at night.)
- Continue to eat a healthy diet and exercise.
- Do not take more than one tablet per day.
- To make sure MEVACOR™ OTC is working, get a fasting cholesterol test at 6 weeks, while continuing to take MEVACOR™ OTC daily.
  - If at 6 weeks your LDL "bad" cholesterol is higher than 129 mg/dL, stop taking MEVACOR™ OTC. Talk to your doctor. MEVACOR™ OTC may not be enough for you.
  - If at 6 weeks your LDL "bad" cholesterol is 1-129 mg/dL, it's working, keep taking it daily and test your cholesterol once a year. If you stop, your cholesterol will go back up.
  - For information on cholesterol testing, talk to your pharmacist or doctor.

Inactive ingredients Butylated hydroxyanisole (BHA), cellulose, FD&C blue No. 2 aluminum lake, lactose, magnesium stearate, and starch.

Other information See inside package for additional information or call toll free 1-800-XXX-XXXX to reach a product specialist or visit us on the web at www.xxxxxxx.com. If after buying this product you decide it is not right for you, return it for a full refund.

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Mevacor OTC Booklet Update
3/24/04

Visit us often
at www.xxxxxxx.com

Questions?
Call a Product Specialist
at 1-800-XXX-XXXX.

MEVACOR™
Lovastatin 20mg OTC

Get your LDL cholesterol to 129 or below... and keep it down.

your guide to Heart Healthy Living

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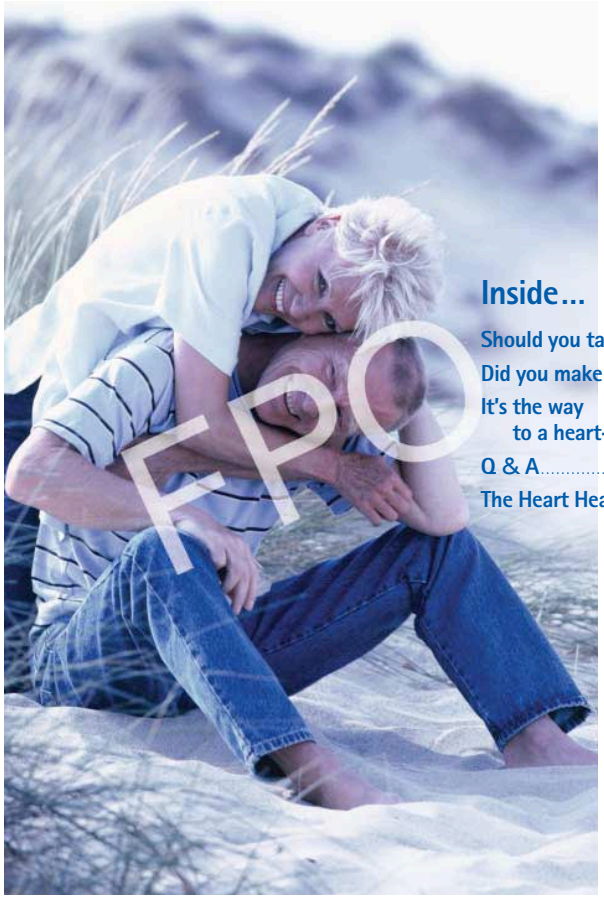


Inside...

Welcome!

You made a smart move when you decided to take action to lower your cholesterol. This booklet will help you understand how to get started, and highlight important steps along the way to better heart health. You'll also learn more about cholesterol, the causes of high cholesterol, and how diet, exercise and MEVACOR™ OTC can help to reduce it.

The way to a heart-healthy life.

Taking control of your heart health includes lifestyle changes and MEVACOR™ OTC. We can help you reach the goal and stay in control... and that can mean a world of difference to you and those who love you.

Read this booklet carefully to learn about how MEVACOR™ OTC can work for you.

Five easy steps to begin lowering your cholesterol

1. **Double-check to make sure it's right for you.**
2. **Test at 6 weeks.**
3. **See if your LDL 6 week test result is 1–129.**
4. **Two things to watch for… every day.**
5. **Enroll in the MEVACOR™ OTC Heart Health Program!**

If you have already referred to the Quick Start Guide and enrolled in the MEVACOR™ OTC Heart Health Program, turn to page 12 for more information about cholesterol and heart-healthy living.

Should you take it?

1 Double-check to make sure it's right for you.

Ask yourself just once more...

MEVACOR™ OTC is not right for everyone. Review this information once again to see if you should take it.

People who have YES (blue) ANSWERS to ALL 5 of the following can take MEVACOR™ OTC.

1. Are you a man 45 years or older or a woman 55 years or older?
   - ☐ NO - STOP. Do not use. Ask your doctor or pharmacist.
   - ☐ YES - Continue.
2. Is your LDL "bad" cholesterol before use 130-170 mg/dL?
   - ☐ NO - STOP. Do not use. Ask your doctor or pharmacist.
   - ☐ YES - Continue.
3. Do you have one or more of these conditions that increase your risk of heart disease? (If yes to any, you may need MEVACOR™ OTC.)
   - You are a smoker (may need MEVACOR™ OTC) **OR**
   - Your HDL "good" cholesterol is 1-39 mg/dL (too low) **OR**
   - You have high blood pressure **OR**
   - You have a family history of heart disease:
     - your father or brother had a heart attack/angina before 55
     - your mother or sister had a heart attack/angina before 65
   - ☐ I have none of the above or I'm not sure/don't know. STOP. Do not use. Ask your doctor or pharmacist.
   - ☐ Yes, I have one or more of the above. Continue.
4. Are you free of ALL of the following conditions?
   - Pregnant or breast-feeding
   - Liver disease
   - Diabetes
   - Had a stroke
   - Allergy to lovastatin
   - HDL of 60-200 mg/dL
   - Ever had a heart attack or angina
   - Taking any prescriptions
   - Taking any other cholesterol-lowering medicine
   - High triglycerides of 200-900 mg/dL
   - Had any muscle pain from a cholesterol-lowering medicine.
   - ☐ I have one or more of the above or I am not sure – STOP. Do not use. Ask your doctor or pharmacist.
   - ☐ I have none of the above – Continue.
5. ☐ **I HAVE A YELLOW ANSWER: STOP Do not use. Talk to your doctor or pharmacist. Return product for a full refund.**
   ☐ **I HAVE ALL YES (blue) ANSWERS: I can use MEVACOR™ OTC.**

Did you make it?

2 Test at 6 weeks.

You're on your way.

Take one tablet daily with your evening meal to lower your LDL "bad" cholesterol.

After 6 weeks of daily use, MEVACOR™ OTC will have lowered your LDL as much as it can.

That's why at 6 weeks, you need to get a fasting cholesterol test.

For best results, fast for a minimum of 9 hours before your test (no food or beverages – water only).

Don't stop taking MEVACOR™ OTC. *Keep taking* it every day so it *keeps working* while you wait for your test results.

For test information:

- ASK your pharmacist or doctor.
- CALL 1-800-XXX-XXXX to reach a product specialist or
- VISIT www.xxxxxxx.com

Did you use your reminder label from the Quick Start Guide?

3 easy ways to get your 6 week cholesterol test.

Remember to fast for a minimum of 9 hours before your test (no food or beverages– water only).

Select the option that's best for you:

1. Consult your pharmacist.

- Some pharmacies may have on-site cholesterol testing available.

2. Contact a local lab.*

- Check your local Yellow Pages under "Laboratories – Medical" to find a lab near you.
- Call to make an appointment for a full lipid profile.

3. Call your doctor's office.

- Contact your doctor to schedule a cholesterol test (a full lipid profile) or ask for a referral to a lab near you.

Questions?

Contact MEVACOR™ OTC Customer Service
at 1-800-XXX-XXXX or visit www.xxxxxxx.com.
Your MEVACOR™ OTC Product Specialist can recommend convenient testing options near you.

* Laboratory testing requirements may differ from state to state.

Did you make it?

3 See if your LDL 6 week test result is 1-129.

Get to the required 6 week goal: LDL "bad" cholesterol 1-129.

In 6 weeks, you'll be able to see how much MEVACOR™ OTC is able to lower your LDL.

At this point, your LDL must be 1-129.

Experts agree that LDL "bad" cholesterol of 129 or below can lower your risk of a first heart attack or stroke.

Your LDL 6 week test result is the only number you need to see if you made it.

See if you made it… "Yes" or "No"?

No 6 week LDL test result is higher than 129.

STOP Stop taking MEVACOR™ OTC.

You should not expect further LDL reduction from continued use. It won't go any lower.

That's why it's important to talk to your doctor as soon as possible.

MEVACOR™ OTC may not be enough for you.

You may need a prescription medicine.

Yes 6 week LDL test result is 1-129.

Great... keep taking MEVACOR™ OTC every day to keep your LDL cholesterol at 129 or below.

If you stop, your cholesterol will go back up.

It's the way to a heart-healthy life.

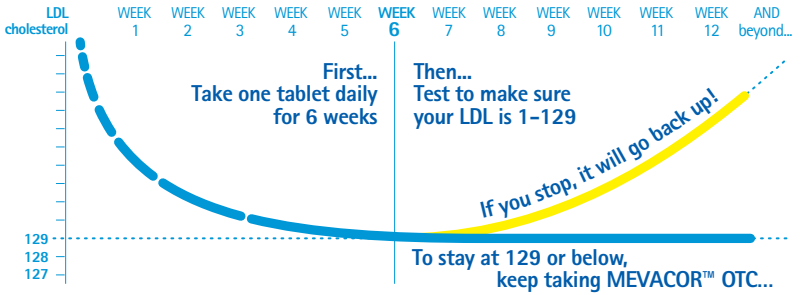
Get your LDL down to 1-129... and keep it down!

Once you've lowered your LDL "bad" cholesterol to 1-129 mg/dL, you're on your way to heart-healthy living. That's because experts agree that an LDL level of 1-129 can lower your risk of a first heart attack or stroke.

Eat healthy, exercise, and continue to take MEVACOR™ OTC every day. You must take one tablet each and every day. Test once a year to make sure you keep your LDL at 129 or below.

Remember to take MEVACOR™ OTC every day.

You can't change the fact that your body makes too much LDL "bad" cholesterol, but by taking MEVACOR™ OTC daily and following a healthy diet and exercise, you can keep it under control... it's the way to a heart-healthy life!



This chart is for illustration purposes only. Your results may vary.

4 Two things to watch for... every day.

Check 2 see!

Certain prescription medicines may interact with MEVACOR™ OTC.

If you are prescribed any new medicines, remember to tell your doctor or pharmacist you are taking MEVACOR™ OTC.

A list of medicines that can interact with MEVACOR™ OTC is provided in the package insert.

Any unexplained muscle pain or weakness in any part of your body could be a sign of a rare but serious side effect.
Stop using immediately.
Call your doctor.

If there is a change in your health...

Talk to your doctor.

As you already know, MEVACOR™ OTC is not meant for people with diabetes or those who have had a stroke or a heart attack.

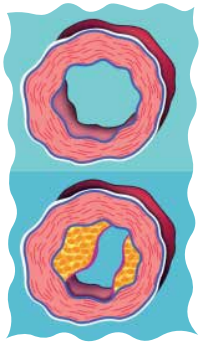
If, while you are taking MEVACOR™ OTC, you are diagnosed with a new medical condition, or you are prescribed a new medicine, tell your doctor you are taking MEVACOR™ OTC.

Remember... you should not be taking MEVACOR™ OTC if:

- You have liver disease.
- You discover you have an allergy to lovastatin, the active ingredient in MEVACOR™ OTC, or the inactive ingredients in this medicine, as listed on the back of the package.
- You are, or plan to become, pregnant. Or, you start breast-feeding.

It's the way to a heart-healthy life.

Understanding cholesterol...



A normal artery

An artery with a buildup of plaque

You can take control.

Your body needs a certain amount of cholesterol to function (to build cells, for example). However, too much of the wrong kind, LDL "bad" cholesterol, can cause health problems, especially for your heart and blood vessels.

That's because high LDL cholesterol, like high blood pressure, can be a slow, silent killer. An elevated LDL level, left untreated over time, can cause a buildup of plaque inside your arteries and increase your risk of a first heart attack or stroke. You may have no symptoms until it's too late.

For more information about your heart and heart disease, visit www.americanheart.org or www.merckhomeedition.com

LDL cholesterol
It's the number that counts!

Cholesterol… "good" vs. "bad."

Cholesterol is a fat-like substance produced in your liver. It can also be found in a number of foods. Here are some quick facts about cholesterol:

Total cholesterol: Your total cholesterol includes both LDL "bad" cholesterol and HDL "good" cholesterol, as well as triglycerides and some additional factors. While your total cholesterol is important, experts agree that your LDL "bad" cholesterol is the most important number to watch when it comes to your heart health.

LDL "bad" cholesterol: It can stick to your arteries, causing a buildup of plaque and obstructing the flow of oxygen to your heart. Taking MEVACOR™ OTC should reduce "bad" cholesterol.

HDL "good" cholesterol: It helps remove the "bad" (LDL) cholesterol from your arteries. That's why a higher HDL cholesterol level is desirable. Taking MEVACOR™ OTC may increase "good" cholesterol.

Triglycerides: Another form of fat in your bloodstream. The bulk of your body's fat tissue is in the form of triglycerides. Many people with high triglycerides also have high LDL or low HDL levels, which increase the risk of heart disease.

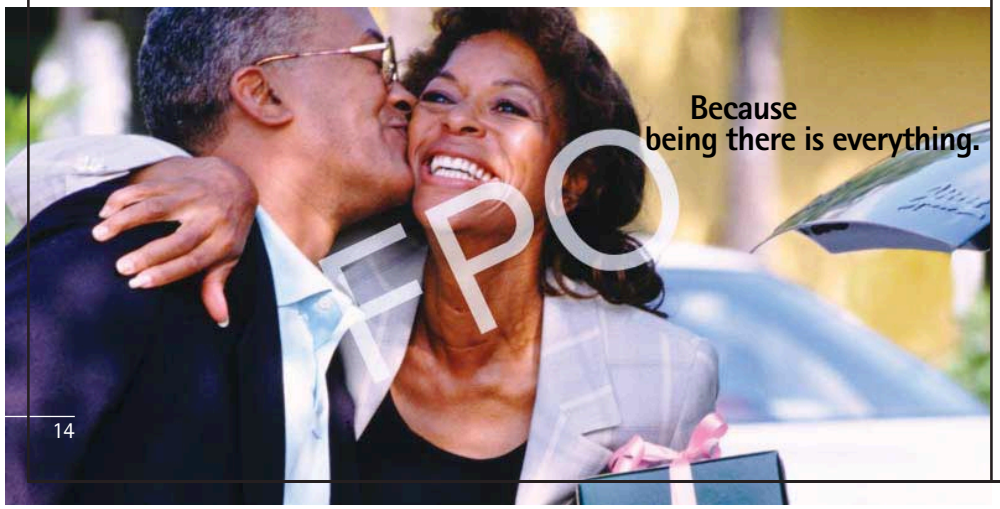
It's the way to a heart-healthy life.

What causes high cholesterol?

While certain foods and a sedentary lifestyle can contribute to high cholesterol, some individuals simply have higher cholesterol than others. For all of these individuals, high cholesterol should be managed, just like diabetes or high blood pressure.

That's why once you begin taking MEVACOR™ OTC, you need to keep taking it every day, even after your LDL cholesterol drops to the recommended goal of 1-129 mg/dL.

The only way you can keep your LDL at 1-129 is by taking MEVACOR™ OTC daily as part of a cholesterol management program that includes a healthy diet and regular exercise.



MEVACOR™ OTC can make a difference.

The ingredient in MEVACOR™ OTC has been prescribed by doctors for over 15 years. Millions of people have used it successfully to lower and control their cholesterol.

Take 1 tablet daily.

It's best to take MEVACOR™ OTC with your evening meal. That's because your body produces more cholesterol at night. MEVACOR™ OTC helps to control the amount of LDL cholesterol produced by your liver.

If you miss a dose, don't double up.

If you forget to take your MEVACOR™ OTC, DO NOT try to "make up" by taking a double dose the next day. Just wait for the next night and resume your normal pattern.

Remember, in order for MEVACOR™ OTC to work for you, you need to take ONE TABLET DAILY. It won't work if you take it only once in a while or when you feel you've eaten too much of the wrong foods.

It's the way to a heart-healthy life.

The role of diet and exercise.

MEVACOR™ OTC can help lower your LDL cholesterol level, but you need to maintain a healthy lifestyle as well, including exercise and a low-fat, low-cholesterol diet. In fact, government guidelines now suggest that you should get no more than 7% of your daily calories from saturated fat. These guidelines also recommend eating more soluble fiber – the kind found in beans, cereal grains, and many fruits and vegetables.

Changing your eating habits may prove to be a challenge at first, but there are plenty of resources available to help you make the switch to a heart-healthy diet. Visit the American Heart Association web site (www.americanheart.org) for a wide variety of recipes, grocery-shopping tips, dining-out strategies and more. Eating healthy, along with taking MEVACOR™ OTC daily, can help lower your LDL cholesterol to 129 mg/dL or below.

Get active!

Regular physical activity is a great way to help control your cholesterol. Exercise helps to control weight and to increase your HDL "good" cholesterol. It also helps to lower your LDL "bad" cholesterol and triglycerides.

You can get a lot of the "exercise" you need from everyday living. Activities such as gardening, walking the dog, house cleaning or yard work – they all count! 20 minutes of moderate exercise 3 times a week can make a big difference. Some people also choose to join a gym or use home fitness equipment.

NOTE: Check with your doctor before beginning any exercise program.

Control these other risk factors

- Check your blood pressure regularly.
- Quit smoking.
- Lose those extra pounds.

And remember to take your MEVACOR™ OTC daily!

Q&A

Frequently Asked Questions About MEVACOR™ Lovastatin 20mg OTC

Q: I'm a 48-year-old male and my total cholesterol is 242 mg/dL. I'm not sure of my LDL and HDL levels. Are they really that important?

A: Absolutely! You need to know ALL of your numbers to see if MEVACOR™ OTC is right for you. If you have been tested within the past year, you can make a phone call to your doctor to get your numbers. Remember to ask for four important numbers:

- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides

Q: After checking all my numbers and the rest of the information on the package, I've determined that MEVACOR™ OTC is right for me. But if my doctor felt my cholesterol was high enough to require medicine, wouldn't he have given me a prescription?

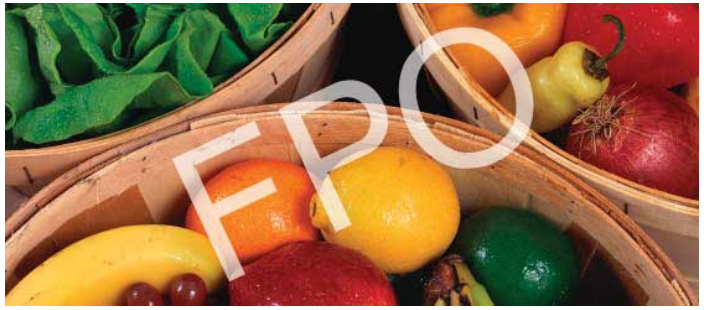
A: Not necessarily. Most likely your doctor suggested trying a healthy diet and exercise first to lower your cholesterol. MEVACOR™ OTC is for people like you, with moderately high LDL cholesterol, who would like to take a more active role to lower it. We suggest you advise your doctor that you are taking MEVACOR™ OTC.

Q: Will I feel better if I take MEVACOR™ OTC?

A: High cholesterol is not a condition you can feel... until it's too late. Cholesterol builds up slowly in your arteries and, over time, restricts the flow of blood and oxygen to your heart. This can lead to chest pain, known as "angina", and may ultimately result in a heart attack or stroke. MEVACOR™ OTC, along with a healthy diet and exercise, can help lower your LDL cholesterol and keep it down.

Q: Once I start taking MEVACOR™ OTC, can I eat whatever I want?

A: No. MEVACOR™ OTC is part of a complete cholesterol management program that includes a healthy diet and exercise. Your medicine should work with, and not instead of, a healthy diet and regular exercise.



Q&A

Q: Why isn't MEVACOR™ OTC right for everyone?

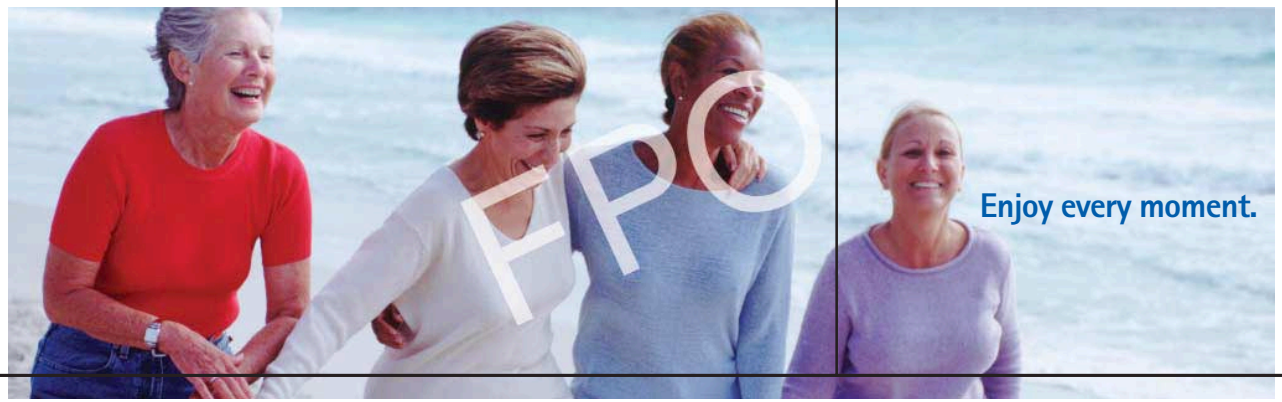
A: MEVACOR™ OTC is appropriate only for those people who meet all of the conditions listed on the back of the package. Other people with higher cholesterol levels or health concerns may need prescription strength medicine or further medical care. These people must talk to their doctors before they can begin taking MEVACOR™ OTC.

Q: Once I get my LDL cholesterol down to 129 or below, why can't I stop taking MEVACOR™ OTC?

A: If you stop taking MEVACOR™ OTC, your LDL cholesterol will go back up. High cholesterol isn't a condition that can be "cured," but it can be managed. MEVACOR™ OTC, along with a healthy diet and exercise, can help you keep it under control.

Q: My LDL cholesterol was 162 when I began taking MEVACOR™ OTC. I've taken it every day for six weeks, watched my diet, and exercised three times a week. When I got tested again, my LDL was 135. What should I do?

A: Stop taking MEVACOR™ OTC. Remember, getting "close" doesn't count. Your LDL must be 1-129 to keep taking MEVACOR™ OTC. After 6 weeks, MEVACOR™ OTC will have lowered your LDL cholesterol as much as it can. It will not go any lower, and you should not expect further LDL reduction from continued use. That's why it's important to talk to your doctor as soon as possible. You may need a prescription medicine.



MEVACOR™ Lovastatin 20mg OTC

Important...

Enroll in the MEVACOR™ OTC Heart Health Program!

MEVACOR® OTC Heart•Health PROGRAM

It's the way to a heart-healthy life.

The MEVACOR™ OTC Heart Health Program is a complete guided plan that helps you to reach the goal and stay in control. It includes ongoing support, timely reminders, lifestyle tips and special values.

3 easy ways to enroll in the Heart Health Program:

- CALL 1-800-XXX-XXXX to reach a product specialist or
- VISIT www.xxxxxxx.com or
- USE the pre-paid postcard in the Quick Start Guide

Your Heart Health Program benefits begin immediately... if you haven't enrolled yet, do it now!

Over $25 in savings!

FREE bottle of MEVACOR™ OTC, a $15 value.

$5 savings on a cholesterol test.

FREE video or DVD with more information about controlling your cholesterol.

FREE American Heart Association cookbook.

FREE reminders and bulletins to help keep you on track.

Plus... much more!

Enjoy
the moment.

Imagine...
how great you'll feel!

Wouldn't miss it
for the world.

LDL "bad" cholesterol... the number that counts!

Today, experts agree that LDL "bad" cholesterol, NOT total cholesterol, is the most vital cholesterol number to watch when it comes to your heart health.

LDL is called "bad" cholesterol because over time, it can cause a buildup of plaque in your arteries, and obstruct the flow of oxygen to your heart.

You've made
a smart move.

Imagine what better heart health will mean to those who love you.

Visit us often
at www.xxxxxxx.com

Questions?
Call a Product Specialist
at 1-800-XXX-XXXX.

MEVACOR™ Lovastatin 20 mg OTC

Get your LDL cholesterol to 129 or below... and keep it down.

IMPORTANT...
Read This First!

Quick Start Guide

Should you take it?

Did you make it?

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MEVACOR™ Lovastatin 20 mg OTC

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MEVACOR™ Heart•Health PROGRAM

Pull out the cards.
Enjoy all the benefits!

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Enjoy
the moment.

Imagine...
how great you'll feel!

Wouldn't miss it
for the world.

Heart•Health PROGRAM

Should you take it?

1 Double-check to make sure it's right for you.

Ask yourself just once more...

MEVACOR™ OTC is not right for everyone. **People who have YES (blue) ANSWERS to ALL 5 of the following can take it:**

1. Are you a man 45 years or older or a woman 55 years or older?
   - ☐ NO - STOP. Do not use. Ask your doctor or pharmacist.
   - ☐ YES - Continue.
2. Is your LDL "bad" cholesterol before use 130–170 mg/dL?
   - ☐ NO - STOP. Do not use. Ask your doctor or pharmacist.
   - ☐ YES - Continue.
3. Do you have one or more of these conditions that increase your risk of heart disease? (If yes to any, you may need MEVACOR™ OTC.)
   - You are a smoker (may need MEVACOR™ OTC) **OR**
   - Your HDL "good" cholesterol is 1–39 mg/dL (too low) **OR**
   - You have high blood pressure **OR**
   - You have a family history of heart disease:
     – your father or brother had a heart attack/angina before age 55
     – your mother or sister had a heart attack/angina before age 65
   - ☐ I have none of the above or I'm not sure/don't know. STOP. Do not use. Ask your doctor or pharmacist.
   - ☐ Yes, I have one or more of the above. Continue.
4. Are you free of ALL of the following conditions?
   - Pregnant or breast-feeding
   - Liver disease
   - Diabetes
   - Had a stroke
   - Allergy to lovastatin
   - HDL of 60–200 mg/dL
   - Ever had a heart attack or angina
   - Taking any prescriptions
   - Taking any other cholesterol-lowering medicine
   - High triglycerides of 200–900 mg/dL
   - Had any muscle pain from a cholesterol-lowering medicine
   - ☐ I have one or more of the above or I am not sure – STOP. Do not use. Ask your doctor or pharmacist.
   - ☐ I have none of the above – Continue.
5. ☐ **I HAVE A YELLOW ANSWER:** STOP **Do not use. Talk to your doctor or pharmacist. Return product for a full refund.**
   ☐ **I HAVE ALL YES (blue) ANSWERS:** I can use MEVACOR™ OTC.

Did you make it?

2 Test at 6 weeks.

You're on your way.

Take one tablet daily to lower your LDL "bad" cholesterol.

After 6 weeks of daily use, MEVACOR™ OTC will have lowered your LDL as much as it can.

That's why at 6 weeks, you need to get a fasting cholesterol test.

Don't stop taking MEVACOR™ OTC.

Keep taking it every day so it *keeps working* while you wait for your test results.

Place this reminder on your calendar.
Mark the date,
6 weeks from the day you take your first tablet.

For test information:
- **ASK your pharmacist or doctor.**
- **CALL 1-800-XXX-XXXX to reach a product specialist or**
- **VISIT www.xxxxxxx.com**

3 See if your LDL 6 week test result is 1–129.

Get to the required 6 week goal: LDL "bad" cholesterol 1–129.

In 6 weeks, you'll be able to see how much MEVACOR™ OTC is able to lower your LDL. At this point, your LDL must be 1–129.

Experts agree that LDL "bad" cholesterol of 129 or below can lower your risk of a first heart attack or stroke.

Your LDL 6 week test result is the only number you need to see if you made it.

See if you made it... "Yes" or "No"?

No **6 week LDL test result is higher than 129.**

STOP **Stop taking MEVACOR™ OTC.**
You should not expect further LDL reduction from continued use. It won't go any lower.

That's why it's important to talk to your doctor as soon as possible.
MEVACOR™ OTC may not be enough for you. You may need a prescription medicine.

Yes **6 week LDL test result is 1–129.**

Great... keep taking MEVACOR™ OTC every day to keep your LDL cholesterol at 129 or below.

If you stop, your cholesterol will go back up.

It's the way to a heart-healthy life.

4 Two things to watch for... every day.

Check 2 see!

Certain prescription medicines may interact with MEVACOR™ OTC.

If you are prescribed any new medicines, remember to tell your doctor or pharmacist you are taking MEVACOR™ OTC.

Any unexplained muscle pain or weakness in any part of your body could be a sign of a rare but serious side effect.
Stop using immediately. Call your doctor.

5 Important... enroll in the Heart Health Program!

Enroll now...
get your next bottle FREE!

The MEVACOR™ OTC Heart Health Program is a complete guided plan that helps you reach the goal and stay in control. It includes ongoing support, timely reminders, lifestyle tips, and special values:

3 easy ways to enroll in the MEVACOR Heart•Health PROGRAM
- **CALL 1-800-XXX-XXXX to reach a product specialist or**
- **VISIT www.xxxxxxx.com or**
- **USE the enclosed pre-paid postcard**

Get over **$25** in savings!

FREE bottle of MEVACOR™ OTC, a $15 value.
$5 savings on a cholesterol test.
FREE American Heart Association cookbook.
FREE reminders and bulletins to help keep you on track.
Plus... much more!

6 Tell your doctor and pharmacist & start your program today!

Should you take it?

1 Double-check to make sure it's right for you.

Ask yourself just once more...

MEVACOR™ OTC is not right for everyone. **People who have YES (blue) ANSWERS to ALL 5 of the following can take it:**

1. Are you a man 45 years or older or a woman 55 years or older?
   - ☐ NO - STOP. Do not use. Ask your doctor or pharmacist.
   - ☐ YES - Continue.
2. Is your LDL "bad" cholesterol before use 130-170 mg/dL?
   - ☐ NO - STOP. Do not use. Ask your doctor or pharmacist.
   - ☐ YES - Continue.
3. Do you have one or more of these conditions that increase your risk of heart disease? (If yes to any, you may need MEVACOR™ OTC.)
   - You are a smoker (may need MEVACOR™ OTC) **OR**
   - Your HDL "good" cholesterol is 1-39 mg/dL (too low) **OR**
   - You have high blood pressure **OR**
   - You have a family history of heart disease:
     - your father or brother had a heart attack/angina before age 55
     - your mother or sister had a heart attack/angina before age 65

   ☐ I have none of the above or I'm not sure/don't know. STOP. Do not use. Ask your doctor or pharmacist.
   ☐ Yes, I have one or more of the above. Continue.
4. Are you free of ALL of the following conditions?
   - Pregnant or breast-feeding
   - Liver disease
   - Diabetes
   - Had a stroke
   - Allergy to lovastatin
   - HDL of 60-200 mg/dL
   - Ever had a heart attack or angina
   - Taking any prescriptions
   - Taking any other cholesterol-lowering medicine
   - High triglycerides of 200-900 mg/dL
   - Had any muscle pain from a cholesterol-lowering medicine

   ☐ I have one or more of the above or I am not sure – STOP. Do not use. Ask your doctor or pharmacist.
   ☐ I have none of the above – Continue.
5. ☐ **I HAVE A YELLOW ANSWER: STOP Do not use. Talk to your doctor or pharmacist. Return product for a full refund.**
   ☐ **I HAVE ALL YES (blue) ANSWERS: I can use MEVACOR™ OTC.**

Did you make it?

2 Test at 6 weeks.

You're on your way.

WEEK 1
WEEK 2
WEEK 3
WEEK 4
WEEK 5
WEEK 6

Take one tablet daily to lower your LDL "bad" cholesterol.

After 6 weeks of daily use, MEVACOR™ OTC will have lowered your LDL as much as it can.

That's why at 6 weeks, you need to get a fasting cholesterol test.

Don't stop taking MEVACOR™ OTC.

Keep taking it every day so it *keeps working* while you wait for your test results.

Place this reminder on your calendar.
Mark the date,
6 weeks from the day you take your first tablet.

For test information:
- **ASK your pharmacist or doctor.**
- **CALL 1-800-XXX-XXXX to reach a product specialist or**
- **VISIT www.xxxxxxx.com**

3 See if your LDL 6 week test result is 1-129.

Get to the required 6 week goal: LDL "bad" cholesterol 1-129.

In 6 weeks, you'll be able to see how much MEVACOR™ OTC is able to lower your LDL. At this point, your LDL must be 1-129.

Experts agree that LDL "bad" cholesterol of 129 or below can lower your risk of a first heart attack or stroke.

Your LDL 6 week test result is the only number you need to see if you made it.

See if you made it... "Yes" or "No"?

No 6 week LDL test result is higher than 129.

STOP Stop taking MEVACOR™ OTC.
You should not expect further LDL reduction from continued use. It won't go any lower.

That's why it's important to talk to your doctor as soon as possible.

MEVACOR™ OTC may not be enough for you. You may need a prescription medicine.

Yes 6 week LDL test result is 1-129.

Great... keep taking MEVACOR™ OTC every day to keep your LDL cholesterol at 129 or below.

If you stop, your cholesterol will go back up.

It's

4

It's the way to a heart-healthy life.

4 Two things to watch for… every day.

Check 2 see!

Certain prescription medicines may interact with MEVACOR™ OTC.

If you are prescribed any new medicines, remember to tell your doctor or pharmacist you are taking MEVACOR™ OTC.

Any unexplained muscle pain or weakness in any part of your body could be a sign of a rare but serious side effect.
Stop using immediately. Call your doctor.

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$5 savings on a cholesterol test.
FREE American Heart Association cookbook.
FREE reminders and bulletins to help keep you on track.
Plus... much more!

6 Tell your doctor and pharmacist & start your program today!

Give to your doctor & pharmacist

Give this card to
your doctor
to update
your medical file.

MEVACOR™ Lovastatin 20 mg OTC

Get your LDL cholesterol to 129 or below... and keep it down.

Give this card to
your pharmacist
to help you avoid the possibility
of drug interactions.

MEVACOR™ Lovastatin 20 mg OTC

Get your LDL cholesterol to 129 or below... and keep it down.

This card is for
you
to keep a record of
your cholesterol test.

MEVACOR™ Lovastatin 20 mg OTC

Get your LDL cholesterol to 129 or below... and keep it down.

Give to your doctor & pharmacist

I am taking MEVACOR™ OTC **(lovastatin 20 mg).**

Name _____

Date I began taking MEVACOR™ OTC / / Test Date / /

My latest cholesterol test numbers were:

LDL-Cholesterol (mg/dL) _____

HDL-Cholesterol (mg/dL) _____

Triglycerides (mg/dL) _____

Total Cholesterol (mg/dL) _____

Drug Interaction Warnings: Itraconazole (SPORANOX®*), Ketoconazole, Erythromycin, Clarithromycin (BIAXIN®*), Protease inhibitors, Nefazodone (SERZONE®*), Cyclosporine, Gemfibrozil (LOPID®*), Niacin (daily doses of 1,000 mg or more). *Registered trademark of their respective owners and not Merck & Company, Inc.

I am taking MEVACOR™ OTC **(lovastatin 20 mg).**

Name _____

Help me avoid drug interactions with MEVACOR™ OTC.

I began taking MEVACOR™ OTC (lovastatin 20 mg) on _____

I am also taking the following medicines

Prescription medicines _____

Over-the-Counter medicines _____

Drug Interaction Warnings: Itraconazole (SPORANOX®*), Ketoconazole, Erythromycin, Clarithromycin (BIAXIN®*), Protease inhibitors, Nefazodone (SERZONE®*), Cyclosporine, Gemfibrozil (LOPID®*), Niacin (daily doses of 1,000 mg or more). *Registered trademark of their respective owners and not Merck & Company, Inc.

Date I began taking MEVACOR™ OTC / / Test Date / /

LDL-Cholesterol (mg/dL) _____

HDL-Cholesterol (mg/dL) _____

Triglycerides (mg/dL) _____

Total Cholesterol (mg/dL) _____

Questions?
Call our Product Specialist at 1-800-XXX-XXXX

Send for a FREE video or DVD

MAIL-IN CERTIFICATE	EXPIRES XX/XX/XXXX

If you'd like to know more... FREE video or DVD.

We'll send you a free video or DVD with more information about controlling your cholesterol with MEVACOR™ OTC... absolutely FREE. Just complete the information below.

Complete this information and mail this postage-paid card: (please print)

Check one: ☐ Video ☐ DVD

Name _____

Address _____

City _____ State ____ Zip _____

E-mail _____

NOTE: Offer good only in U.S.A. and APO/FPO addresses. This request form may not be mechanically reproduced. LIMIT ONE MEVACOR™ OTC FREE VIDEO OR DVD OFFER PER HOUSEHOLD. No group or organization requests will be honored. Your offer rights may not be transferred or assigned. Offer void where prohibited or taxed. Please allow 1-2 weeks for receipt of the free video/DVD.

Send for a FREE video or DVD

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 433 HORSHAM PA
POSTAGE WILL BE PAID BY ADDRESSEE

HEART HEALTH PROGRAM
PO BOX 625
HORSHAM PA 19044-9816

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES

Enroll in the program now!

FREE when you enroll

Please contact me about enrolling in the MEVACOR™ OTC Heart Health Program.
Enrollment entitles me to:

- **FREE** bottle of MEVACOR™ OTC, a $15 value.
- **$5 savings** on a cholesterol test.
- **FREE** American Heart Association cookbook.
- **FREE** reminders and bulletins to help keep you on track.
- **FREE** video or DVD with more information about controlling my cholesterol.

Complete the following information and mail this postage-paid card:
(please print)

Name _____

Address _____

City _____ State _____ Zip _____

Phone _____

E-mail _____

NOTE: Offer good only in U.S.A. and APO/FPO addresses. This request form may not be mechanically reproduced. LIMIT ONE MEVACOR™ OTC FREE ENROLLMENT OFFER PER HOUSEHOLD. No group or organization requests will be honored. Your offer rights may not be transferred or assigned. Offer void where prohibited or taxed. Please allow 1-2 weeks for receipt of the free video/DVD.

Enroll in the program now!

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 433 HORSHAM PA
POSTAGE WILL BE PAID BY ADDRESSEE

HEART HEALTH PROGRAM
PO BOX 625
HORSHAM PA 19044-9816

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES

First-Time Buyers

Should you take it?

Use this guide to find out.

1 Any questions, ask the study personnel – don't guess.

2 First, find out your exact numbers

- Call your doctor and ask (if tested within the last year).
- Ask study personnel for information on cholesterol testing.

Write your exact fasting cholesterol numbers in the 4 boxes below:

NOTE: Don't confuse TOTAL with LDL "bad" cholesterol.

1. Total cholesterol	_____ Total is good to know, but is NOT as important as LDL to decide if MEVACOR™ OTC is right for you.		
2. LDL "bad" cholesterol	_____ 1-129 DO NOT USE	_____ 130-170	_____ 171-400 DO NOT USE
3. HDL "good" cholesterol	_____ 1-59	_____ 60-200 DO NOT USE	
4. Triglycerides	_____ 1-199	_____ 200-900 DO NOT USE	

Are your numbers right for MEVACOR™ OTC?

ALL BLUE NUMBERS?	ANY YELLOW NUMBERS?
See reverse side.	STOP Must not use. Talk to your doctor or study personnel

Should you take it?

3 People who have BLUE ANSWERS to ALL 5 of the following can take MEVACOR™ OTC:

1. Do you have all blue numbers from other side?

☐ NO – STOP. Do not use. Ask your doctor or study personnel.

☐ YES – Continue.

2. Are you a man 45 years or older or a woman 55 years or older?

☐ NO – STOP. Do not use. Ask your doctor or study personnel.

☐ YES – Continue.

3. Do you have one or more of these conditions that increase your risk of heart disease? (If yes to any, you may need MEVACOR™ OTC)

- You are a smoker (may need MEVACOR™ OTC) **OR**
- Your HDL "good" cholesterol is 1-39 mg/dL (too low) **OR**
- You have high blood pressure **OR**
- You have a family history of heart disease:
  - your father or brother had a heart attack/angina before age 55
  - your mother or sister had a heart attack/angina before age 65

☐ I have none of the above or I'm not sure/don't know. STOP. Do not use. Ask your doctor or study personnel.

☐ Yes, I have at least one of the above – Continue.

4. Are you free of ALL of the following conditions?

- Pregnant or breast-feeding
- Liver disease
- Diabetes
- Had a stroke
- Allergy to lovastatin
- Ever had a heart attack or angina
- Taking any prescriptions
- Taking cholesterol medicine
- HDL of 60-200 mg/dL
- Triglycerides of 200-900 mg/dL
- Had any muscle pain from a cholesterol-lowering medicine

☐ I have one or more of the above or I am not sure. STOP. Do not use. Ask your doctor or study personnel.

☐ I have none of the above – Continue.

5.

☐ **I HAVE A YELLOW ANSWER:** STOP
Do not use. Talk to your doctor or study personnel.

☐ **I HAVE ALL YES (blue) ANSWERS:**
You can use MEVACOR™ OTC.
Read back of package carefully.

Repeat Buyers

Did you make it?

Use this guide to find out.

1 Did you get a fasting cholesterol test at 6 weeks?

If not, ask the study personnel for test information.

2 Did you get to the required 6 week goal: LDL 1–129?

If not, ask the study personnel before you buy. At 6 weeks, you need to get a fasting cholesterol test to see if you should continue taking MEVACOR™ OTC.

If you have not had your 6 week test, see below. OR If you know your results, see reverse side.

Schedule your cholesterol test now.

1. Ask the study personnel for information on cholesterol testing.
2. Use your $5 savings. Call 1-800-MEVACOR (638-2267) for details.

Your LDL 6 week test result must be 1–129 for you to continue taking MEVACOR™ OTC.

LDL test result is the number you need – see step 3 on back.

Questions? Call 1-800-MEVACOR or visit www.mevacorstudy.com

Review your LDL test result… did you make it?

When you get your results, write your LDL cholesterol number in the correct box below.

3 Use this guide to see if you made it…"Yes" or "No"?

Remember, getting "close" doesn't count. Your LDL must be 1–129 to keep taking MEVACOR™ OTC.

LDL 130–170

No 6 week LDL test result is higher than 129.

STOP **Stop taking MEVACOR™ OTC.**
You should not expect further LDL reduction from continued use. *It won't go any lower.*

That's why it's important to talk to the study doctor or study personnel as soon as possible.
MEVACOR™ OTC may not be enough for you. You may need a prescription medicine.

LDL 1–129

Yes 6 week LDL test result is 1–129.

Keep taking MEVACOR™ OTC every day to keep your LDL cholesterol at 129 or below…
If you stop, your cholesterol will go back up.

Congratulations, you've reached the goal!
MEVACOR™ OTC has helped to reduce your risk of a first heart attack or stroke. Continue to take MEVACOR™ OTC every day to keep your LDL under control. It's the way to a heart-healthy life!


Zocor Heart-Pro®
10mg tablets
28 tablets
HR 20816 240504
Zocor Heart-Pro®
10mg tablets
28 tablets
® denotes registered trademark & ™ denotes trademark of Merck & Co. Inc., Whitehouse Station, NJ, USA.
© Johnson & Johnson • MSD Consumer Pharmaceuticals 2004. All rights reserved.
Zocor Heart-Pro®
10mg tablets (simvastatin)
Effectively reduces the risk of a heart attack
✓ Helps to reduce build up of plaques in arteries
✓ Significantly lowers cholesterol levels
28 tablets now available without a prescription
HHP™ Healthy Heart Programme
Batch No:
Expiry Date:
Zocor Heart-Pro®
10mg tablets
28 tablets
20816 240504
5 027097 280035
P
PL 13249/0039
Johnson & Johnson • MSD CONSUMER PHARMACEUTICALS
High Wycombe, Buckinghamshire HP10 9UF
For further information e-mail:
zocor@jnjmsd.co.uk
Each Zocor Heart-Pro® film-coated tablet contains 10 mg simvastatin.
Simvastatin belongs to a group of medicines known as statins which significantly reduce the amount of cholesterol in your blood. Too much cholesterol in your blood builds up in the walls of the arteries and causes plaques to form. This can lead to a narrowing of the coronary arteries, just like hard water furs up a water pipe. Heart attacks can then happen when a blood clot forms in a narrowed coronary artery.
Zocor Heart-Pro® is for people who have a moderate risk of coronary heart disease (heart disease due to build up of plaques in the coronary arteries). Moderate risk means your chances of having a heart attack in the next 10 years are at least 1 in 10. Your Pharmacist can advise you further and help you to identify your risk level.
DOSAGE:
Swallow one tablet every evening. Do not take more than one tablet each day.
Do not take Zocor Heart-Pro® if: you know that you have liver disease, or you know that you have abnormal liver function blood tests; you could become, are pregnant or breast-feeding; you are allergic to any of the ingredients; you have had muscle problems after taking a cholesterol lowering medicine in the past; you are taking itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin or nefazodone or if you are already taking a prescription cholesterol lowering medicine.
Please read the enclosed patient information leaflet for important safety information.
Do not store the tablets above 30°C.
Keep them out of the reach and sight of children.

Zocor Heart-Pro®

10mg tablets
(simvastatin)

PLEASE READ THIS LEAFLET CAREFULLY BEFORE YOU START TO TAKE YOUR TABLETS. KEEP IT IN CASE YOU WANT TO READ IT AGAIN.

WHAT IS ZOCOR HEART-PRO®?

Each film-coated tablet contains 10mg simvastatin as the active ingredient.

The tablets also contain ascorbic acid (E300), butylated hydroxyanisole (E320), citric acid monohydrate (E330), lactose, magnesium stearate (E572), microcrystalline cellulose (E460), pregelatinised maize starch, hydroxypropylcellulose (E463), methylhydroxypropylcellulose (E464), talc (E533b), titanium dioxide (E171), red iron oxide (E172) and yellow iron oxide (E172).

Zocor Heart-Pro® tablets come in calendar packs containing 28 film-coated tablets.

The marketing authorisation holder is: Johnson & Johnson•MSD Consumer Pharmaceuticals, Enterprise House, Station Road, Loudwater, High Wycombe, Buckinghamshire HP10 9UF.

Product Licence Number: PL 13249/0039

Manufacturer: Merck Manufacturing Division, Merck Sharp and Dohme Limited, Northumberland NE23 3JU, UK.

WHAT IS ZOCOR HEART-PRO® FOR?

Zocor Heart-Pro® tablets can reduce the risk of heart attack in people who have a moderate risk of coronary heart disease (heart disease because of build up of plaques in the coronary arteries). Moderate risk means your chances of having a heart attack in the next 10 years are at least 1 in 10.

The active ingredient in Zocor Heart-Pro®, simvastatin, belongs to a group of medicines known as statins. These significantly reduce the amount of cholesterol in your blood. Zocor Heart-Pro® reduces the level of LDL (bad) cholesterol and fatty substances called triglycerides in your blood and raises HDL (good) cholesterol. LDL cholesterol is called "bad" cholesterol because it is the cholesterol that clogs your coronary arteries. HDL is called "good" cholesterol because it helps to protect against heart disease. Too much cholesterol in your blood builds up in the walls of the coronary arteries causing plaques to form. This leads to a narrowing of the coronary arteries, just like hard water furs up a water pipe. Heart attacks can then happen when a blood clot forms in a narrowed coronary artery.

Taking these tablets can significantly reduce cholesterol levels and help to reduce build-up of artery-narrowing plaques. In order to benefit from treatment, these tablets should be taken regularly on a long-term basis. The risk of heart attacks increases as you age because of the build up of plaques. Reducing this risk with these tablets and changes to your lifestyle needs to be a lifelong effort.

Zocor Heart-Pro® reduces the levels of bad cholesterol in the blood by around 27%. Studies show that reducing cholesterol by this much can reduce the risk of a heart attack by about one third after 3 years of treatment.

You are likely to be at moderate risk if you are a man aged 55 or over.

You are also likely to be at moderate risk if you are a man aged between 45 and 54 or a woman aged 55 or over and you answer yes to one or more of the questions below:

- Do you have a parent, brother or sister who suffered a heart attack younger than 55 for men or 65 for women?
- Do you smoke or have you smoked within the past 5 years?
- Are you overweight? This means you have a body mass index over 25 kg/m^2 (your weight in kilos divided by your height in metres squared), or your waist is greater than 40 inches or 102 cm (for men), or 35 inches or 88 cm (for women). Your pharmacist can help you answer this question.
- Are you of South Asian origin i.e. from the Indian subcontinent that includes India, Bangladesh, Pakistan or Sri Lanka?

If, in addition, you take no physical exercise other than normal daily activities, your risk of a heart attack is further increased.

WHAT ELSE CAN I DO TO REDUCE MY RISK OF A HEART ATTACK?

At the same time as taking Zocor Heart-Pro® tablets, try to reduce your risk of coronary heart disease by doing the following:

- Stop smoking - there is strong evidence to link cigarette smoking with heart disease. The risks increase with the number of cigarettes you smoke each day, but risks still exist even if you smoke as little as five a day. It is better to stop smoking altogether rather than just cut down on how much you smoke. Your pharmacist can advise you on a suitable programme to help you stop smoking.
- Eat a healthy diet - a healthy diet will not only help towards preventing coronary heart disease, but has also been shown to reduce the risk of stroke and a number of cancers. Try to increase the amount of fruit and vegetables in your diet and reduce the amount of sugar, salt and fat.
- Lose weight - being overweight can cause a rise in your blood pressure, increases your risk of developing diabetes and increases the risk of developing heart disease due to high cholesterol levels. Change your diet as described previously and take more exercise.
- Exercise - a brisk walk to the shops can help. Swimming is a good all-round exercise that you could consider doing, as it is something you can gradually build up without overdoing it to start with. You could try adding the following to your daily routine: vigorous housework, walk upstairs more often (and don't take the lift or escalator when you are out), and gardening.

Your pharmacist can provide details of a Healthy Heart Programme to help you.

For more information e-mail: zocor@jnjmsd.co.uk.

IS ZOCOR HEART-PRO® RIGHT FOR ME?

Do not take these tablets if you:

- know you have liver disease or you have been told you have abnormal liver function blood tests;
- drink more than 4 units of alcohol a day for men and 3 units of alcohol a day for women (one unit is 1/2 pint of lager, a pub measure of wine or one short);
- have had an allergic reaction to this or similar medicines or to any of the ingredients in the past;
- are already taking prescription drugs to lower your cholesterol;
- could become pregnant, are pregnant, are planning to become pregnant, or are breast feeding;
- discover you are pregnant while taking Zocor Heart-Pro®. In this case you should stop taking these tablets immediately and contact your doctor;
- have had muscle problems in the past after taking a cholesterol lowering medicine;
- are taking one of the following medicines:
  - oral antifungal medicines called itraconazole or ketoconazole.
  - antibiotics called erythromycin, telithromycin or clarithromycin.
  - medicines for HIV infections called protease inhibitors (such as indinavir, nelfinavir, ritonavir or saquinavir).
  - the antidepressant nefazodone.

If you have an under active thyroid gland (hypothyroidism), kidney problems, a family history of muscle disorders or are aged over 70, you should check with your doctor before taking this product.

This product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Zocor Heart-Pro® should not be used by children.

If you are in one of the groups below, you are at a higher risk of coronary heart disease. You should discuss your condition with your doctor since you are likely to need more than these tablets to reduce your risk.

- You already have angina or have had a heart attack.
- You have diabetes.
- You have had a stroke.
- You have disease of the arteries of your legs or neck.
- You have inherited (it runs in the family) very high blood cholesterol levels.

If you would like to receive other advice and information on a healthy lifestyle and reducing your risk of a heart attack, register onto the Healthy Heart Programme overleaf.

Zocor Heart-Pro®
10mg tablets

HHP™ Healthy Heart Programme

79878/280504

If you think any of these apply to you or you are unsure that you have one of these conditions, go and talk to your pharmacist or doctor first.

If your doctor has told you that you have high blood pressure, check with your doctor before taking Zocor Heart-Pro®.

If you have your cholesterol levels checked and you find that you have a fasting LDL-cholesterol measurement greater than 5.5 mmol/l, you should talk to your doctor because you may need more than Zocor Heart-Pro® to reduce your cholesterol levels.

BEFORE YOU TAKE ZOCOR HEART-PRO®

If you are taking any other medicines, speak to your pharmacist before taking Zocor Heart-Pro®.

DRIVING AND ZOCOR HEART-PRO®

This product can cause dizziness. If affected, do not drive or operate machinery.

WHILE YOU ARE TAKING ZOCOR HEART-PRO®

Very rarely, these tablets can affect the muscles. If this problem develops, it can be serious especially if you continue to take the drug. Stop taking your tablets immediately and check with your doctor if you develop generalised muscle pain, tenderness or weakness, unless it is clearly the result of flu, unaccustomed exercise, or recent strain or injury.

The chance of your muscles being affected is greater if you drink a lot of grapefruit juice, (see below) or if you have kidney problems or are taking certain medicines.

In addition to the medicines listed in the section "Is Zocor Heart-Pro® right for me?" this medicine can react with the following drugs to cause muscle problems:

- Ciclosporin (an immunosuppressant medicine).
- Prescription cholesterol-lowering medicines (such as bezafibrate, gemfibrozil and high doses of niacin or nicotinic acid (more than 1000mg/day)).

If you go into hospital for major surgery, tell your doctor you are taking Zocor Heart-Pro® as you will need to stop taking it a few days beforehand.

If your skin or whites of your eyes turn yellow or your urine appears very dark in colour, this may mean that you have a liver problem. So, stop taking your tablets and see your doctor.

WHAT ELSE DO I NEED TO KNOW?

Grapefruit juice contains one or more substances that alter the metabolism of some medications, such as Zocor Heart-Pro®. Do not drink very large quantities (more than 1 litre a day). However, just drinking one 250 ml glass a day is unlikely to cause problems.

DOES ZOCOR HEART-PRO® REACT WITH OTHER MEDICINES?

In addition to the medicines listed in the section "While you are taking Zocor Heart-Pro®", other medicines may cause problems when you take them with these tablets.

These are:

- medicines for thinning the blood, such as warfarin
- high doses of niacin or nicotinic acid (more than 1000 mg a day) for poor blood flow to the hands or feet.

If you are taking any prescription medicine, your pharmacist may advise you to check with your doctor before taking Zocor Heart-Pro®. If your doctor prescribes a new medicine for you while you are taking this product (for example, if you develop an infection and your doctor decides to give you a course of antibiotics), you should mention that you are taking Zocor Heart-Pro®.

WHAT IS THE DOSE OF ZOCOR HEART-PRO®?

Take one tablet every evening. Swallow the tablet with a drink of water. The evening is the best time because it means that your medicine will be working when your body is producing the most cholesterol. Zocor Heart-Pro® should be taken regularly and on a long-term basis in order to gain the full benefits of treatment.

Never take more than one tablet each day.

If you forget a dose, just take one dose the next evening you remember. Do not take an extra one to make up.

If you take too many tablets by mistake, contact your doctor or pharmacist.

CHECKING YOUR CHOLESTEROL

If you have a moderate risk of heart disease, reducing the level of cholesterol in your blood will reduce your risk. Your pharmacist can arrange to check your cholesterol level, but it is not necessary to know this before you start Zocor Heart-Pro®. Checking your cholesterol can provide additional information and can be helpful to show your progress while taking Zocor Heart-Pro®. If your fasting LDL-cholesterol measurement is above 5.5 mmol/l, speak to your doctor.

WHAT ABOUT SIDE EFFECTS?

Like all medicines, Zocor Heart-Pro® may occasionally cause side effects in some people. The most common side effects are stomach upsets (such as sickness, stomach pain, constipation, diarrhoea, and flatulence (wind)), rash, itchiness, weakness, headache or indigestion. The following have also occurred: hair loss, dizziness, abdominal pain, tingling and numbness, abnormal blood test results for liver and muscle function.

Rarely, a few patients have experienced the following: liver disease (e.g., yellowing of the skin or the whites of your eyes, dark coloured urine), muscle disease (aches and pains) which can be severe (see "While you are taking Zocor Heart-Pro®" section), or an allergic reaction. The allergic reaction may include: swelling of the face or neck, muscle and joint pains, joint and blood vessel inflammation, itchy, lumpy rash, (hives, nettle rash), a high temperature, flushing, difficulty in breathing, or tiredness.

If any of these happen to you, or you have any other unusual symptoms or feelings, stop taking the tablets and contact your doctor or pharmacist **immediately**.

HOW SHOULD I STORE THE TABLETS?

Do not store your tablets above 30°C. Keep them out of the sight and reach of children. Do not put them in another container as they might get mixed up. Do not take them after the expiry date on the blister and carton.

REMEMBER this medicine is for you. Do not share it with anyone else. It may not suit them.

Date the leaflet was prepared: May 2004.

If you would like to receive other advice and information on a healthy lifestyle and reducing your risk of a heart attack, register onto the

Healthy Heart Programme.

Please give your explicit consent for us to contact you by filling in the form. Cut along the dotted line, put it in an envelope and return to the FREEPOST address below (no stamp required).
This will give us permission to contact you.

Name _____

Address _____

_____

_____

_____

Email: _____

Johnson & Johnson • MSD
CONSUMER PHARMACEUTICALS
FREEPOST, High Wycombe, HP10 9UF

HHP™ Healthy Heart Programme

79878/280504

ZOCOR HEART-PRO RECOMMENDATION ADVICE

Remember, to reduce your risk of a heart attack, you must continue to take Zocor Heart-Pro every day.

As well as Zocor Heart-Pro, your pharmacist has given you advice on:

- ☐ Stopping Smoking
- ☐ Increasing Exercise
- ☐ Losing weight

For further information and help, visit www.heartpro.co.uk or call the Zocor Heart-Pro nurse helpline on 0800 0000000.

Remember, tell your pharmacist or doctor if:

- You notice any change in your health, particularly chest pain that comes on with exertion (e.g. on walking), or if you develop new symptoms.
- You develop generalised muscle pain, tenderness or weakness, unless it is the result of flu, unaccustomed exercise, or a recent strain or injury.

When you see your doctor, remember:

- To mention that you are taking Zocor Heart-Pro, especially if your doctor prescribes any new medicines.

Zocor Heart-Pro™ USER CARD

Show to your pharmacist whenever reordering Zocor Heart-Pro

Always read the pack leaflet and tell your pharmacist of any change in your health.

Let your doctor know you are on Zocor Heart-Pro at your next visit.

For further information on the Healthy Heart Programme visit www.heartpro.co.uk

Zocor Heart-Pro™
USER CARD

Show to your pharmacist whenever reordering Zocor Heart-Pro

Always read the pack leaflet and tell your pharmacist of any change in your health.

Let your doctor know you are on Zocor Heart-Pro at your next visit.

For further information on the Healthy Heart Programme visit www.heartpro.co.uk

TO BE COMPLETED BY YOUR PHARMACIST :

PHARMACY NAME AND ADDRESS

DATE OF FIRST PURCHASE

__ __ . __ __ . __ __

PRIVATE AND CONFIDENTIAL

Heart Health
Customer Questionnaire

PLEASE ANSWER ALL QUESTIONS BELOW BY TICKING THE BOXES. IF YOU ARE NOT SURE ABOUT ANY OF THE QUESTIONS, LEAVE IT BLANK AND THE PHARMACIST WILL HELP YOU.

1. ABOUT YOU...

Are you:

Male ☐ 45-54 years ☐ 55 and over

Female ☐ 55 and over

Yes ☐ No ☐ If female, have you reached the menopause?

☐ None of the above - Talk to the pharmacist before going further

Do any of the following risk factors apply to you?

Yes ☐ No ☐ Current smoker, or smoker within the last year

Yes ☐ No ☐ Family history of early heart disease:
- father or brother had a heart attack or angina* before age 55
- mother or sister had a heart attack or angina* before age 65

**angina is heart pain felt in the chest brought on by exercise or exertion*

Yes ☐ No ☐ Overweight: *Your pharmacist can help with this if you know your height, weight and waist measurement*

Yes ☐ No ☐ Family origin from South Asia (e.g. India, Pakistan, Bangladesh, Sri Lanka)

Height:		ft/in or m/cm
Weight:		stones/kg
Waist:		in or cm

2. ABOUT YOUR MEDICAL HISTORY...

Do any of the following apply to you?

Your doctor has told you that you have or have had:

Yes ☐ No ☐ Diabetes

Yes ☐ No ☐ Heart problems (e.g. heart attack or angina); a stroke; peripheral vascular disease (e.g. painful poor blood flow to the legs)

Yes ☐ No ☐ A condition called 'familial hypercholesterolaemia' (or FH) – a very high cholesterol level that runs in families

Yes ☐ No ☐ High blood pressure that your doctor has prescribed tablets for
If you haven't had your blood pressure checked within the last 6 months, your pharmacist may be able to offer you a check

Yes ☐ No ☐ Any of these conditions: liver disease or abnormal liver tests in the past; muscle problems that run in your family (e.g. muscular dystrophy); porphyria (a very rare condition that runs in families); an underactive thyroid gland; kidney problems

If you are unsure about any of these, please ask the pharmacist

Do any of the following apply to you?

Yes ☐ No ☐ You have recently had unexplained heart or chest pain brought on by exercise or exertion

Yes ☐ No ☐ Your average daily intake of alcohol is more than 4 units/day (men), or 3 units/day (women)
(1 unit = 1/2 pint of beer, 1 small glass of wine or 1 pub measure of spirits)

Yes ☐ No ☐ You drink grapefruit juice in large amounts (more than 1 litre daily)

Yes ☐ No ☐ You have been prescribed cholesterol-lowering medicine in the past

Yes ☐ No ☐ You are taking medicine prescribed by your doctor

Please write down the name(s) of any medicines you are taking, or if you are unsure of the name(s), discuss it with the pharmacist:

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