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November 8, 2007

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LCDR, U. S. Public Health Service
Program Management Officer
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5630 Fishers Lane, Rockville MD, 20857

Dear Dr. Ngo:

NDA 21-213: MEVACOR™ Daily Tablets
(Nonprescription lovastatin 20 mg)

ADVISORY COMMITTEE BACKGROUND PACKAGE
AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Reference is made to the New Drug Application (NDA) cited above, submitted as an electronic archive on December 10, 1999, by Merck Research Laboratories (MRL), a division of Merck & Co., Inc.; and to a Complete Response to the Not Approvable Letter (dated February 23, 2005) submitted on July 26, 2007. The original application provided for a 10 mg nonprescription (over-the-counter, OTC) form of lovastatin for the treatment of elevated cholesterol for primary prevention of coronary heart disease. The August 2004 resubmission supported use of nonprescription lovastatin 20 mg (as an adjunct to diet and exercise) in otherwise healthy individuals with elevated low density lipoprotein cholesterol (130-170 mg/dL) and multiple risk factors of coronary heart disease. The July 2007 resubmission provided new information on Labeling, Clinical Safety and Consumer Behavior, and Chemistry, Manufacturing and Controls. Reference is also made to an August 30, 2007 electronic mail message from Ms. Diem-Kieu Ngo, Pharm.D., Program Management Officer, FDA Advisors and Consultants Staff, to Edwin L. Hemwall, Ph.D., Executive Director, MRL, advising of the need and timing for the background package.

In accordance with the Federal Advisory Committee Act (FACA) and FDA's regulations governing disclosure of information concerning New Drug Applications in 21 CFR 314.430, and the February 2007 Draft Guidance, "Guidance for Industry Advisory Committee Meetings – Preparation and Public Availability of Information Given to Advisory Committee Members", MRL is submitting forty electronic CD copies in Adobe PDF and twenty paper copies of the MEVACOR™ Daily Tablets Advisory Committee Background Package **available for public disclosure without redaction** for distribution to the Advisory Committee and FDA staff

members in preparation for the upcoming Antiviral Drugs Advisory Committee Meeting. A copy of the Final Background Package has been simultaneously submitted to Andrea Leonard-Segal, M.D., Director, Center for Drug Evaluation and Research, Division of Nonprescription Clinical Evaluation for the official files.

This Background Package provides a summary of consumer behavior and label comprehension study results, as well as safety and efficacy information, which supports the proposed approval of MEVACOR™ Daily Tablets (nonprescription lovastatin 20 mg) for the treatment of elevated cholesterol for primary prevention of coronary heart disease. Most information contained in this document was included in official submissions previously made to NDA 21-213.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.*

All of the information is contained on one Compact Disk (CD) and is not more than 300MB. MRL has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

Questions concerning this supplemental application should be directed to Brenda A. McGuire, M.S. R.N., (267-305-7071) or, in my absence, to Edwin L. Hemwall, Ph.D., (267-305-8406).

Sincerely,

Brenda McGuire

Brenda A. McGuire, M.S., R.N.
Associate Director
Worldwide OTC Regulatory Affairs

Desk copies: Ms. Diem-Kieu Ngo, Pharm.D. (20 paper copies and 40 CDs)

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INTRODUCTION

Despite the availability of effective treatments, coronary heart disease (CHD) remains a leading cause of disability and mortality in the United States. Primary prevention of CHD prevents a cascade of subsequent events that represent a substantial economic burden in the U.S. Elevated cholesterol is one of the major risk factors for CHD and lipid lowering treatment has been demonstrated to be effective for primary prevention of CHD. The National Heart, Lung and Blood Institute has issued the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III Guidelines for the treatment of hypercholesterolemia. The guidelines call for lifestyle changes, specifically appropriate diet and exercise. If such changes fail, pharmacologic therapy is recommended and statins are the mainstay of pharmacologic therapy. However, despite universal endorsement of the ATP III Guidelines by all major medical organizations, a profound cholesterol treatment gap still exists.

The availability of a nonprescription statin is anticipated to help narrow the treatment gap. Consumers already attempt to manage their cholesterol by purchasing unproven food and dietary remedies and the availability of a statin would give them the option of purchasing an effective pharmacologic alternative. MEVACOR™ Daily (lovastatin 20 mg) is an appropriate choice for a nonprescription statin. MEVACOR™ (lovastatin), the first statin to be approved by FDA in 1987, now has 20 years of experience in doses ranging from 10 to 80 mg. Efficacy and safety have been well-established through the vast marketed use of the product as well as by the post-approval megatrials, the Expanded Clinical Evaluation of Lovastatin (EXCEL) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).

In 1997 Merck & Co., Inc. undertook what was probably the most challenging nonprescription development program ever attempted. Since then, the MEVACOR™ Daily development program has progressed through three NDA submissions. The program has satisfactorily addressed a number of long-standing issues relating to the safety, efficacy and target population of lovastatin 20 mg, as evidenced by the highly positive Advisory Committee votes on these topics at the January 13-14, 2005 joint Advisory Committee deliberations. The remaining issues, identified by FDA following the January 2005 Advisory Committee Meeting, center around consumers' ability to appropriately self-select for use of the product based on label information. With the resubmission of the NDA in July 2007, Merck is now seeking regulatory approval to market MEVACOR Daily 20 mg. The resubmission was primarily comprised of the results of a self-selection study (SELECT) and two label comprehension studies. These studies were conducted to address the specific issues identified by FDA and focused on learning why consumers made decisions, since an informed, thoughtful choice could be accepted even if outside the conservative label criteria.

GUIDE TO THE READER

This Background document provides a summary of the continued development program that was undertaken in support of the New Drug Application (NDA) for MEVACOR™ Daily 20 mg. All of the information contained in this summary has been extracted from documents included in the July 2007 NDA Resubmission or the January 2005 Advisory Committee Meeting Background Document. Although the same data were used, the presentation of some of the same information may differ from that presented in the regulatory submission.

A. Overview: This section is an overview of the information contained in the full document, and is intended to orient the reader to the key elements of the more detailed presentation that follows. It provides a summary of the MEVACOR™ Daily "story", including:

- the rationale for a nonprescription statin
- the well-established safety and efficacy profile of prescription lovastatin
- consumer behavior and label comprehension, focusing on the results of the SELECT self-selection study and two label comprehension studies which were conducted to address the specific issues identified by FDA following the 2005 Advisory Committee Meeting
- the elements of a marketing plan which has been designed to provide information and ongoing support to consumers making responsible decisions on initial purchase and continued use of the product
- the benefit and risk conclusions of making MEVACOR™ Daily 20 mg available without a prescription.

The sections following the Overview provide more detailed information in each of these areas.

B. Consumer Behavior: This section describes the evolution of the treatment paradigm and of the OTC label based on FDA input and findings from the SELECT and CUSTOM studies, as well as two new Label Comprehension studies which focused on improving label messaging in key areas. Learnings from these studies have helped to shape the product label and other support materials that are now under consideration in the NDA application for nonprescription lovastatin 20 mg. Importantly, the key area where results from SELECT could be improved with better labeling is identified at the end of the Results section. Also included at the end of this Consumer Behavior section is a manuscript authored by Dr. Eric Brass on the SELECT study, entitled "Can consumers appropriately self-select for appropriate use of an over-the-counter statin? The Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT) study".

C. MEVACOR™ Daily Self Management System and Market Monitoring Plan: Merck has developed a comprehensive, collaborative care approach designed to direct consumer behavior in safe, responsible and appropriate decision-making on the inclusion of an OTC statin in their self-managed cholesterol-lowering efforts. This section describes the various "tools" included in the overall MEVACOR™ Daily Self-Management System and the postmarketing plans to maintain such a support system after the product's launch. In addition, an educational campaign will be undertaken to raise awareness and knowledge

levels of healthcare professionals who will have the opportunity to interact with and advise consumers on their decision-making. Finally, Merck and its marketing partner, GlaxoSmithKline (GSK), commit to implementing a comprehensive in-market monitoring program to track consumer usage patterns and will, as necessary, adjust the self-management system in order to improve consumer understanding of safety and benefit.

D. Benefit and Risk Conclusions: The potential benefits of nonprescription lovastatin, estimation of cardiovascular risk and risk reduction in the OTC-eligible population, the potential risks of nonprescription therapy, as well as how these risks are managed through labeling and other package materials, are all discussed in this section. In addition, this section brings together the conclusions that can be drawn from the extensive safety, efficacy, and consumer behavior data available after many years of clinical and postmarketing experience with lovastatin.

E. Glossary of Abbreviations: To assist the reader in understanding the many medical, professional and organizational acronyms that appear throughout the document, a complete list of abbreviations and the accompanying terms or names are provided in alphabetical order.

F. List of References: A list of references, denoted in the text by numbers in brackets [ ], follows the Glossary of Abbreviations. These citations refer only to publicly available publications.

G. Appendices: Those publications which Merck feels are of particular importance in furthering the reader's understanding of the overall nonprescription statin paradigm and MEVACOR™ Daily program are provided here. A number of relevant articles as well as graphic images of MEVACOR™ Daily packaging and labeling are included. In addition, Summary sections excerpted from the Jan 2005 Advisory Committee Meeting's Briefing document on Safety, Efficacy, and Pharmacokinetics & Drug Metabolism of lovastatin are provided here for the convenience of the reader.

A. OVERVIEW

A. OVERVIEW

Merck & Co., Inc. pioneered statin development, obtaining FDA approval in August 1987 for prescription lovastatin (MEVACOR™), the first drug of the statin class. Since the time of first approval until 31-Dec-2006, there has been a total estimated exposure to lovastatin of approximately 35 million patient-treatment years in doses ranging from 10 to 80 mg per day, with the majority of prescriptions being written for the 20-mg dose. In 1997 Merck initiated the nonprescription, or over-the-counter (OTC), switch development program for lovastatin. Since then, the MEVACOR™ Daily (lovastatin 20 mg) development program has progressed through two NDA submissions, which satisfactorily addressed a number of long-standing issues relating to the safety and efficacy of lovastatin 20 mg, as evidenced by the positive Advisory Committee votes on these topics at the January 13-14, 2005 joint Advisory Committee deliberations. The remaining issues identified by FDA in a post-Advisory Committee NDA Action Letter center around consumers' ability to appropriately self-select for use of the product based on label information. There was particular interest in improving messaging in the areas of use by women less than 55 years, women of childbearing potential, low coronary heart disease (CHD) risk consumers, and avoidance of muscle toxicity. As a result, the primary focus of this background document is on the results of the self-selection study titled **S**elf **E**valuation of **L**ovastatin to **E**nhance **C**holesterol **T**reatment (SELECT) and two label comprehension studies (one assessing the outside carton labeling and one assessing all materials warning about the muscle side effect) which were conducted to address these specific issues. Additionally, greater focus was placed on learning why consumers made decisions, since an informed, thoughtful choice could be appropriate for a given individual even if outside the conservative label criteria.

Merck's marketing partner for MEVACOR™ Daily will be GlaxoSmithKline (GSK). GSK has an excellent record of bringing informed access to OTC medicines which address public health issues of smoking and obesity. Merck and GSK commit to the same type of consumer communication and education programs for cholesterol management which equip and support consumers through the behavior modifications that are essential for success with OTC medicines that require long-term changes in lifestyle.

1. Rationale for Nonprescription Lovastatin

Despite the availability of effective treatments, CHD remains a leading cause of morbidity and mortality in the United States. Primary prevention of CHD prevents a cascade of subsequent events that represent a substantial health and economic burden in the U.S. Hypercholesterolemia is one of the major risk factors for CHD and treatment of hypercholesterolemia has been demonstrated to be effective for primary prevention of CHD. The National Heart, Lung and Blood Institute has issued the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III Guidelines for the treatment of hypercholesterolemia (see Appendix 5). The Guidelines call for lifestyle changes, specifically appropriate diet and exercise. If such changes prove inadequate, pharmacologic therapy is recommended and statins are the mainstay of pharmacologic therapy. Despite universal endorsement of the ATP III Guidelines by all major medical

organizations, a profound cholesterol treatment gap still exists (see Section D, Benefit/Risk Assessment and Conclusions for details of the cholesterol treatment gap).

The availability of a statin without a prescription is anticipated to help narrow the cholesterol treatment gap. Consumers already attempt to manage their cholesterol by purchasing unproven food and dietary remedies, and the availability of an OTC statin would give them the option of purchasing an effective pharmacologic therapy. MEVACOR™ Daily (lovastatin 20 mg) is an appropriate choice for an OTC statin. The efficacy and safety of lovastatin has been well-established through the 20 years of marketed use of the product as well as by the post-approval megatrials, the Expanded Clinical Evaluation of Lovastatin (EXCEL) [1] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [2].

Nonprescription Lovastatin Target Population

At the January 2005 Advisory Committee meeting, Committee members unanimously agreed that the proposed OTC target population warranted treatment with a statin to lower cholesterol and thereby reduce heart disease risk.

The population proposed for OTC eligibility is a primary prevention group targeted to be consistent with the current NCEP ATP III Guidelines and was defined in collaboration with FDA and academic experts. The OTC labeling approach used to reach this risk group guides the user to have low density lipoprotein cholesterol (LDL-C) between 130 and 170 mg/dL and two or more CHD risk factors, one of which is age (men ≥45 years, women ≥55 years). By design, the majority of individuals in this group would be expected to achieve ATP III target treatment goals (LDL-C<130 mg/dL) using a low-dose statin without the need for titration. Thus, the upper end of the LDL-C range is capped at 170 mg/dL because individuals with higher levels are unlikely to achieve the 130 mg/dL 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 Appendix 2 for details of lovastatin efficacy). Like the NCEP approach for physicians, the MEVACOR™ Daily label represents a guideline for consumers and should not be viewed as hard cut points, outside of which the product is no longer appropriate. Our studies show that individuals can apply their own medical situation when assessing age and lipid values. Thus, the label works as a surrogate for medicalized guidelines to minimize inappropriate use and maximize use by the right population.

Additionally, the OTC statin-eligible population should not have underlying chronic conditions that complicate self-management. Thus, individuals with active liver disease, 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. Samples of actual carton label and consumer education and support materials are provided in Appendix 4.

2. Safety of Lovastatin

The 2004 NDA submission for nonprescription lovastatin summarized the safety information available from an estimated 27 million patient-years of marketed use since lovastatin was first approved in 1987 to July 2003. These data were reviewed at the

January 13-14, 2005 Advisory Committee meeting. The current application summarizes the information available from an additional estimated 8.1 million patient-years of marketed use in the subsequent 3½ year time period ending December 31, 2006, or an incremental experience approaching 30% of the exposure accumulated during the previous 17 years. The safety information from this period supports the safety profile that has been previously well defined and no new safety signals were identified. Specific areas of potential safety concern are discussed below. For more detailed information see Appendix 1, Summary of Safety for the summary of safety information that was provided to members of the 2005 Advisory Committee meeting.

Muscle

At the January 2005 Advisory Committee meeting, Committee members unanimously agreed that the risk of muscle toxicity with lovastatin 20 mg was acceptably low for an OTC drug. Subsequently, the NDA Action Letter directed that labeling be further enhanced in order to improve compliance with the muscle warning. Label comprehension testing was recommended to document the improvement in the labeling. As a result, the MEVACOR™ Daily inner package materials (Quick Start Guide and Package Insert) were modified to strengthen the communication of the warning about unexplained muscle pain during product use. Also, a "refrigerator magnet" was developed to repeat the muscle warning text and serve as an added reminder for consumers. The magnet will be included with the other internal package materials for MEVACOR™ Daily. All of these materials provide an even more thorough explanation of the condition and possible consequences of not heeding the warning. The revisions were tested in Muscle Warning Comprehension Study #088, where the results included scores exceeding 90% and sometimes 95%. These results clearly showed that consumers understood what they should do in the event that they developed such symptoms (see Section B, Consumer Behavior for a detailed summary of Study #088).

With regards to myopathy (including rhabdomyolysis) the clinical literature continues to support that this is a low incidence adverse event, with resolution upon discontinuation of statin use. While the etiology of statin-induced myopathy is still unclear, the risk factors for its development are much better understood than when this safety issue was first identified. Consequently statin product circulars clearly provide information on the risk with increasing dose and with the use of certain concomitant medications. The 20 mg lovastatin dose proposed for OTC use was shown in clinical trials to have a rate of myopathy that was consistent with that for placebo, and provides an additional safety margin being at the low end of the range of safe prescription doses. However, since the concomitant use of certain medications can increase the risk of myopathy with statins, the information contained in the proposed Drug Facts for MEVACOR™ Daily informs consumers to ask their doctor or pharmacist prior to use if they are taking any of the medications listed therein. The Pivotal Label Comprehension Study #087 summarized in the current NDA submission showed that consumers demonstrated a very high level of understanding of this precautionary language (see Section B, Consumer Behavior for a detailed summary of Study #087).

Liver

At the January 2005 Advisory Committee meeting, Committee members unanimously agreed that liver function testing was not necessary either pretreatment or during treatment with nonprescription lovastatin 20 mg. In April 2005 the recommendation for periodic transaminase testing was removed from the prescription lovastatin product circular for doses less than 40 mg daily.

Possible statin-associated liver effects have also become better understood over time. Asymptomatic transaminase elevations are known to occur with statins although clinical trials with lovastatin 20 mg showed that these occurred with the same frequency as with placebo. There is no evidence that these elevations are predictive of more serious liver disease.

Serious liver disease with statin use has been determined to occur very rarely: the risk of fulminant liver failure with lovastatin has been estimated at 1-2 cases per million patient-years, which is similar to the background rate for the general population. What has remained an issue up until recently, has been lovastatin use in persons with unrecognized liver disease. New studies now support the conclusion that there is no increased risk of statin use in patients with either pre-existing transaminase elevations or with pre-existing chronic liver disease. One study, which reviewed the case records of over 90,000 patients with liver disease, was conducted at FDA's request and is highly supportive of this conclusion. (For details, see Section 6.3.3 of this Overview) Thus, the carefully evaluated hepatic safety profile of lovastatin is consistent with OTC use. Even if there is use of lovastatin in patients with undiagnosed asymptomatic liver disease, there does not appear to be any increased risk to the liver. As an added precaution, the proposed Drug Facts label language for MEVACOR™ Daily informs consumers to consult their physician prior to use if they have known liver disease.

Pregnancy

A risk of fetal toxicity from maternal exposure to lovastatin has not been clearly demonstrated and, if it exists, is likely to be small. At the January 2005 Advisory Committee meeting, most Committee members (in a 19 to 5 vote) agreed that the low potential for harm to the fetus should not prevent OTC status. However, Committee members agreed that the then-proposed OTC label should be improved. As a result, the proposed Drug Facts for MEVACOR™ Daily has been revised to state that women who are pregnant, nursing or who think they may become pregnant (i.e., capable of conceiving and sexually active) should not use this product, and that the product may cause problems in the unborn child. The consumer behavior study SELECT and the Pivotal Label Comprehension Study #087 evaluated consumer understanding of this cautionary language. The results demonstrated that the current labeling was very effective in communicating this contraindication. The currently proposed labeling for MEVACOR™ Daily will result in very low risk of exposure, thus further minimizing this risk.

Lovastatin, like all statins, is Pregnancy Category X on the prescription label, and use during pregnancy is contraindicated. 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 [48] have since shown that the rodent fetal effects are caused indirectly by maternal toxicity associated with the high doses rather than directly by fetal toxicity. 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 demonstrate a pattern of adverse outcomes. There have been rare reports of congenital anomalies with human use although the causal role of lovastatin for these findings is uncertain. Nonetheless, since no benefit of statin use during the period of the pregnancy is anticipated to the mother, lovastatin is contraindicated during pregnancy.

The information regarding use of lovastatin during pregnancy was carefully evaluated. Information on exposure to lovastatin or simvastatin (which is structurally closely related to lovastatin) was obtained from 3 sources of information: the WAES database, the Swedish Medical Birth Registry, and the published clinical literature. The largest case series (of 477 reports) was published by Pollack et al [3]. The authors concluded that no pattern of congenital anomalies was identified and that there was no indication of association between adverse pregnancy outcomes and maternal exposure to lovastatin or simvastatin. No pattern of congenital anomalies was identified across the 3 sources of information listed above. Importantly, all 3 sources included prospectively collected information. Prospective reports are less likely to be influenced by reporting bias and are more likely to reflect pregnancy outcomes in the exposed population as a whole. The Teratogen Information System (TERIS) summary for lovastatin, issued in December 2006, was also obtained. This summary, which was written by a team of clinical teratology experts following a thorough literature review, concluded that the risk of teratogenic effect was "Unlikely."

Overdose and Abuse Potential

The available information on overdose and abuse of lovastatin has also been reviewed. The information on overdosage continues to support the excellent safety profile of lovastatin even when ingested in excessive amounts. There continues to be no evidence of any abuse potential for lovastatin.

Other New Analyses

Since 2005, at FDA request, Merck reviewed all placebo-controlled trials of MEVACOR of 6 months duration or longer to identify any cases of Amyotrophic Lateral Sclerosis (ALS). Data from the following trials were reviewed: AFCAPS/TexCAPS; EXCEL; The Monitored Atherosclerosis Regression Study (MARS); A Canadian Coronary Atherosclerosis Intervention Trial (CCAIT). A total of 10,171 patients randomized to lovastatin therapy 20 to 80 mg provided a total of 23,835 patient years of exposure to lovastatin. There were no cases of ALS.

Safety Summary

In summary, the safety profile of lovastatin 20 mg is well defined. The frequency of serious adverse events is low and in clinical trials was consistent with that seen with placebo treatment. Given this large margin of safety, lovastatin 20 mg has a safety profile that is appropriate for use in a nonprescription (OTC) setting.

3. Efficacy of Lovastatin

At the January 2005 Advisory Committee meeting, the Committee unanimously agreed that lovastatin 20 mg was an appropriate dose to lower cholesterol and reduce heart disease risk in the proposed target population for nonprescription use.

The clinical efficacy of lovastatin in reducing low density lipoprotein cholesterol (LDL-C) was established by many studies, most notably in EXCEL in which lovastatin 20 mg lowered LDL-C by a mean of 24% [1]. The efficacy of lovastatin 20 mg in lowering LDL-C has been confirmed in a nonprescription clinical trial setting with the **C**onsumer **U**se **St**udy of **O**ver-the-Counter **M**EVACOR™ (CUSTOM). In CUSTOM, after 26 weeks of therapy, LDL-C was reduced by 25% (in participants with fasting pre and post LDL-C values) in this open-label, uncontrolled study.

The efficacy of lovastatin for primary prevention of cardiac disease was established by AFCAPS/TexCAPS which demonstrated that lovastatin reduced the risk for first acute major coronary event by 37% after 5 years of treatment [2]. Forty-four percent of the 6605 participants in the study would have been eligible for MEVACOR™ Daily based on the proposed OTC label. A post-hoc analysis of these 2882 patients found that treatment with lovastatin 20 mg or 40 mg reduced the risk for first acute major coronary event by 45% (Risk ratio: 0.545, 95% confidence interval (0.384, 0.775), p=0.001). These results indicate that treatment of consumers at risk of CHD with lovastatin 20 mg would significantly reduce the risk of a CHD event. Complete efficacy results from CUSTOM and the post-hoc analysis of AFCAPS/TexCAPS are provided in Appendix 2.

4. Consumer Behavior

In the previous NDA submission, reviewed by the Advisory Committees in January 2005, the data supporting self-selection and continued use came primarily from the CUSTOM actual use study, and the data supporting persistence with treatment came primarily from an 18-month actual use study of lovastatin 10 mg (Pharmacy Study #076) and the 6-month CUSTOM study. After reviewing these data, the FDA identified two areas where improvement in consumer behavior was necessary: initial self-selection, and the ongoing use decision regarding development of unexplained muscle pain. Therefore, it was agreed that the product labeling would be revised and tested in label comprehension and self-selection studies. The focus of the current submission is these new studies which demonstrate improvement of self-selection behavior, label comprehension of the revised product materials, and strong comprehension of the label elements on unexplained muscle pain.

The ongoing use consumer behavior data obtained from CUSTOM (e.g., follow-up cholesterol test, deselection, compliance and persistence) was accepted by FDA and remain valid and supportive of nonprescription availability of lovastatin (see Section B, Consumer Behavior for a detailed summary).

4.1 Label Comprehension

Following the January 2005 Advisory Committee meeting, revised label text was tested via several qualitative and quantitative pilot studies that included a number of label text alternatives. The key targets for improved self-selection, and hence improved label communication, were women under 55 years old, women who may become pregnant, and individuals at lower risk for heart disease. Learnings from the pilot studies were applied to the final labels tested in the Pivotal Label Comprehension Study #087 and the Muscle Warning Comprehension Study #088. Detailed summaries of these studies are provided in Section B, Consumer Behavior.

4.1.1 Pivotal Label Comprehension (PLC) Study # 087

The PLC Study, using the same label tested in SELECT, was conducted following a pilot program that included substantial quantitative label testing.

The objective of the PLC Study was to measure consumer comprehension of the communication messages on the back label of the MEVACOR™ Daily package, with a primary focus on the Drug Facts section. It tested two different usage paradigms, one based on LDL-C and the other one based on Total-C. The labels that were tested had evolved based on iterative consumer testing as well as FDA input on the usage paradigm and the Drug Facts format.

The study results showed that the MEVACOR™ Daily package label was effective in message communication. Both representative and low literate respondents were able to demonstrate that they understood the key usage directions, warnings, and cautions on the label. Among both the total representative respondents and those in the low literacy subgroup, the most important safety warnings and cautions demonstrated the strongest message communication. In particular, correct or acceptable answers were given by 95% or more of the respondents in both groups for the messages regarding pregnancy, breast-feeding, liver disease, diabetes, and the ongoing-use muscle warning.

The LDL-C and the Total-C labels showed a strong consistency in communication of key messages, with most of the few differences favoring the Total-C label on scenarios that addressed cholesterol values. This likely reflects the greater familiarity that most consumers have with total cholesterol versus LDL cholesterol.

While somewhat lower scores were obtained for messages regarding ongoing use, it is important to note that the key focus of the PLC study was to show improvement in the initial selection decision that consumers make. The results regarding ongoing use cannot be fully interpreted without all package materials and systems being available to the consumer, and these were not included in the PLC study. The ongoing use messages were previously tested in the CUSTOM actual use trial of MEVACOR™ OTC.

4.1.2 Muscle Warning Comprehension Study #088

The objective of the Muscle Warning Comprehension study was to measure consumer comprehension of the warning relating to the possible rare occurrence of unexplained muscle pain, tenderness or weakness following initiation of MEVACOR™ Daily. This study utilized the LDL-C label and the "support" materials found in the package which reinforce and expand upon the muscle warning message. These specific support materials included the Quick Start Guide, the Package Insert, and a "refrigerator message magnet" that could serve as an additional reminder for consumers. The muscle warning text used in the in-package materials has been expanded beyond the concise text found in the Drug Facts label, and includes a more thorough explanation of the condition and the possible consequences of not heeding the warning (see labeling materials in Appendix 4). The study questionnaire was primarily open-ended and included hypothetical scenarios in addition to open-ended questions.

The study results showed that the MEVACOR™ Daily label and in-package materials together were highly effective in communicating the warning about unexplained muscle pain, tenderness, or weakness that could be experienced after one begins using the product. (Results are presented in greater detail in Section B. Consumer Behavior.) The results also showed that participants knew that one should stop using the product and see a doctor if muscle pain symptoms were experienced, that the symptoms could be experienced at any time, that the consequences of ignoring the symptoms could be serious, and that the warning itself is extremely serious. These results were similar both for a representative sample of respondents and for a low literacy sample.

The use of open-ended and probe questions enabled respondents to demonstrate that they understood the essential elements of the warning and could apply them to their own likely behavior. While the data from this unique study cannot be compared directly to CUSTOM, the strong scores for these messages support the conclusion that purchasers of this product will notice, understand, and heed this warning.

4.2 Self-Selection

The CUSTOM study demonstrated that participants could appropriately manage their treatment of cholesterol over time, including treatment to an LDL-C goal, compliance and persistence, and changes in health status (new prescriptions, new medical conditions). It also showed that participants achieved beneficial lipid lowering with MEVACOR™ Daily (see Section B. Consumer Behavior for a detailed summary of CUSTOM results). However, some self-selection results in CUSTOM were targeted for improvement. Specifically, women less than 55 years of age, women of childbearing potential, and people with lower CHD risk required additional focus.

To improve self-selection in these populations, the product package label was revised to increase clarity while retaining the most critical CHD risk assessment factors in NCEP ATP III Guidelines. It focuses on warnings regarding key contraindications, simplified eligibility criteria, and enhanced explanation of likelihood of individual benefit. As requested by the FDA, this revised label was tested in label comprehension studies as

described above and in the SELECT self-selection study. Below is a brief summary of the SELECT Study design and results (a detailed summary of the SELECT Study is provided in Section B, Consumer Behavior). Dr. Eric Brass, who participated in the design and evaluation of the SELECT study, has co-authored a manuscript, and a complete pre-publication draft is included in Section B.3, SELECT Study Manuscript Submitted for Publication.

Key study design aspects of SELECT Study #086:

- "All-comers": exclusions only to limit potential behavior bias (similar to CUSTOM)
- Two-arm: randomization to either LDL-C label paradigm or Total Cholesterol (Total C) label paradigm, and stratified by gender (a Total-C label paradigm was developed and tested because other work has demonstrated that more consumers are familiar with Total-C).
- Multi-center: 7 metropolitan areas in the U.S.; 14 store front study sites (similar to CUSTOM)
- Non-drug: participants were shown prototype market image packages with no actual drug provided. However, participants were unaware that drug would be unavailable until after all decision data were collected.
- Participants were asked to make two self-selection decisions:
    - **Self-assessment (SA) decision:** Is the product appropriate for you to use right now or not?
    - **Purchase decision (PD):** Would you like to pay for the product right now for your own use or put it back in the display?

4.2.1 SELECT Study Results

Overall

A total of 1499 participants completed the study procedures. Of the 1326 participants who were evaluable for self-assessment decision, 72% made a correct decision regarding whether or not the product was appropriate for them. Likewise, of the 1457 participants who were evaluable for purchase decision, 77% made a correct decision whether or not to purchase the product.

The SELECT study showed meaningful improvement in self-selection decisions by women < 55 years of age and childbearing potential, while performing similarly to CUSTOM regarding lower CHD risk consumers. In addition, self selection by participants with safety ineligibilities remained favorably low and comparable to the good scores observed in CUSTOM.

Women ≤55 Years

A small percentage of women <55 years who evaluated the product made incorrect self-assessment (11.1%, 42/377) or purchase decisions (12.4%, 48/387). This is a notable improvement (approximately 50%) over CUSTOM, where 23.5% (161/685) of women <55 years who evaluated the product made an incorrect decision to purchase.

Additionally, of those 48 women who made an incorrect self-assessment decision in SELECT, 44% were within 4 years of age 55.

Women of Childbearing Potential

With this substantial reduction of the percentage of women <55 years of age who would incorrectly self-select to purchase, the product label helps to effectively minimize the number of women of childbearing potential who would be exposed to the drug. Looking at the group of women under 45 years of age (the age where unintended pregnancy is more likely to occur), there was an approximate 70% improvement over CUSTOM (15% of women less than 45 years in CUSTOM elected to use the product versus 5.3% in SELECT).

More importantly, the effectiveness of the revised label was demonstrated by the fact that 100% (26/26) of the women who said they were pregnant, breast-feeding, or may become pregnant correctly decided not to purchase.

Low CHD Risk

Of the participants in SELECT with lower CHD risk (<5% risk of CHD in 10 years, based on Framingham Risk Calculation), 73% (192/263) decided that MEVACOR™ Daily was not appropriate for them and 76.7% (207/270) decided not to purchase the product. To be consistent with CUSTOM, it is necessary to look at the number of participants in SELECT who wanted to purchase (PD=Yes), of which 29% (127/433) were of low CHD risk. In CUSTOM, 27% (289/1059) of the product users had 10-year CHD risk <5%. Thus, despite the marked reduction in women less than 55 years of age who wanted to purchase, SELECT was similar to CUSTOM in the proportion of low CHD risk purchasers.

Of the 536 participants in SELECT with Framingham CHD risk <5% who provided a purchase decision, 409 were females (76.3%) and 127 were males (23.7%). Of the proportion of participants who responded PD=Yes, 48.4% (88/182) of females and 11.4% (27/237) of males had a calculated CHD risk <5%. These results are comparable to CUSTOM, in which 51% of female users and 11% of male users had a calculated CHD risk <5%, and the results indicate that the label properly excluded low-risk males.

Interestingly, the agreed upon label paradigm, endorsed at the 2005 Advisory Committee hearing, actually allows seemingly lower risk people to use the product. The uneven distribution of CHD risk <5% between females and males reflects the Framingham risk calculation in a study cohort largely compliant with the product label. The package label for nonprescription lovastatin was developed to be consistent with NCEP ATP III Guidelines for primary prevention using pharmacologic treatment in males ≥45 years of age or females ≥55 years of age with elevated LDL-C or Total C and a CHD risk factor. Thus, an individual, especially a female, could meet the label criteria for treatment with nonprescription lovastatin, and yet have a <5% 10 year CHD risk according to the Framingham CHD Risk Score calculation. However, new AHA Guidelines recognize that risk in women is often underestimated, and urge a more proactive approach to

treating women, which is not inconsistent with the population defined by the MEVACOR™ Daily label (see Appendix 6).

Table A-1 shows a summary of the above results in the areas targeted for improvement in SELECT compared to the previous CUSTOM results.

Comparison of LDL-C and Total-C Label Paradigms

Two label paradigms were tested in SELECT. One was based on LDL-C and the other was based on Total-C to determine if, given the familiarity of Total-C with consumers, the Total-C label paradigm would generate better consumer decision making behavior.

For participants who said SA=Yes, in the LDL-C paradigm 36% of participants were in the correct LDL-C range, compared to the Total-C paradigm where 50% were in the correct Total-C range. In addition, 28% of participants who said SA=Yes in the LDL-C paradigm did not know their LDL-C values, compared to only 11% of SA=Yes participants in the Total-C paradigm who did not know their Total-C values.

These observed differences favoring the Total-C label may be due to consumers being more familiar with their Total-C values than LDL-C and the Total-C label being more "consumer friendly." However, when the overall proportions of corrects are compared, there is a smaller difference between the labels.

Table A-1
Summary of SELECT and CUSTOM Comparisons

Criteria	SELECT (%)	CUSTOM (%)
Women < 55		
Women <55 electing to use (PD=Yes, incorrect)	12	23.4
Women Users <55 (PD=Yes, incorrect)	25.5	37
Women of Childbearing Potential		
Pregnant or Breastfeeding (PD=No, correct)	100	100
Women <45 electing to use the product (PD=Yes, incorrect)	5.3	15
Low CHD risk Users (PD=Yes) with <5% Framingham risk score	29	27
Low-risk men	11	11
Low-risk women	47.8	51

Safety Criteria

The SELECT study also maintained the high scores based on the safety elements of the label that were achieved in CUSTOM, and demonstrated that, based on purchase decision, 100% of the participants adhered to the label's absolute safety criteria (pregnancy, breastfeeding, childbearing potential, and allergy to lovastatin).

Reasons for Participant Decisions

One of the features of the SELECT study was to collect information to help understand the participants' thought processes when making their self-assessment and purchase decisions by asking many open-ended questions when participants made decisions that would appear to be incorrect. In order to put participants' decisions into perspective, the deviations from label criteria were divided into three categories:

- **Benefit** – age too young, lipid values out of range or unknown, history of stroke or heart disease, current diabetes, planning to substitute MEVACOR™ Daily for current Rx cholesterol medicine, no additional CHD risk factors
- **Relative Safety Contraindications** – taking potentially interacting drugs, current liver disease, planning to take MEVACOR™ Daily concomitantly with current Rx cholesterol medicine, drinking large quantities of grapefruit juice
- **Absolute Safety Contraindications** – allergic to lovastatin, pregnant or breastfeeding, may become pregnant

Most of these decisions in which the participant decided to "override" the label involved benefit criteria, while only a few participants overrode safety criteria (resulting in 100% correct for absolute contraindications and over 90% correct for relative contraindications for purchase decision). The most common "override" for benefit was lipid values. Some participants said they would talk with their doctor about their ineligibility either before buying or before using the product. Participants felt they were still following the label when choosing to do this since the label clearly states, "Ask a doctor or pharmacist before using if…" for all label elements except for the absolute safety elements. Other reasons that offer insight include "told by doctor I should be treated," "I am close to (age, LDL, Total-C, HDL)," "I will get/check my cholesterol numbers before using," and "I have a family history of heart disease."

Differences in SELECT and CUSTOM Study Designs

In CUSTOM, participants had the ability to use decision-making tools including tear pads and decision wheels, and had access to a 1-800 number and a website for advice. Participants in CUSTOM were also given help with eligibility assessments by the investigators playing the role of a pharmacist if the consumer requested it. In addition, participants in CUSTOM were able to leave the site and speak to their doctor for advice and had additional opportunities to get lipid values. Finally, in CUSTOM, participants had access to the educational materials in the box (post purchase). None of these features were available to the participants in SELECT. Consumers in the marketplace would have access to all of these additional program components both pre and post-purchase. Despite the limited information provided to participants, the SELECT study showed notable improvement, demonstrating that participants could make appropriate decisions with the box alone and without their physicians' input.

4.3 Summary of Self-Selection and Actual Use Results

The self-selection data from SELECT, and the actual use data from CUSTOM and the earlier lovastatin use studies (detailed in Section B, Consumer Behavior) all contribute in

some way to the conclusion that consumers can appropriately self-select and deselect to use nonprescription lovastatin, achieve LDL-C lowering and treatment-to-goal rates similar to established prescription benchmarks, and readily partner with their physicians to achieve maximal benefit from drug therapy. Data on long-term persistence and compliance with nonprescription lovastatin therapy indicate that 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. In the 18-month Pharmacy Study #076, 72% of participants remained in the study at 6 months, 57% remained in the study at 12 months, and 49% remained in the study at 18 months. Overall, 76.7% of the participants who continued in the study at 6 months remained in the study through 18 months, indicating 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. These data were confirmed in the 6-month CUSTOM Study where 79% of Users made an appropriate persistence decision. Finally, data from CUSTOM and the Post-CUSTOM Survey demonstrate that the Self-Management System motivates individuals to maintain or improve heart-healthy lifestyle behaviors including diet and exercise.

5. Marketing Plans

Merck and GSK are highly committed to ensuring that proper consumer behavior will be the cornerstone of the MEVACOR™ Daily cholesterol treatment program. This commitment includes the development of the MEVACOR™ Daily Self Management System, a comprehensive approach to ensuring proper consumer behavior in lowering cholesterol. To ensure these results translate into the real-world setting, Merck and GSK are committed to an extensive in-marketing monitoring program that will provide an accurate picture of consumer behavior including self-selection, usage patterns, and de-selection. Results from the in-marketing monitoring program will be shared with FDA on a timely basis and adjustments will be made to the Self Management System, if necessary.

5.1 MEVACOR™ Daily Self-Management System

The Self Management System consists of the following ten items most of which have been tested and demonstrated to be successful in the CUSTOM Actual Use study. For more detailed information see Section C, MEVACOR™ Daily Self-Management System and Marketing Plans.

1. **Limited Marketplace Distribution**: to licensed pharmacies or other licensed healthcare clinics where trained healthcare professionals are available to assist consumers in the proper selection or de-selection of the product.
2. **Consumer-Directed Communications**: Advertising and promotion will be balanced and responsible. It will be targeted only towards consumers who are appropriate to use the product.

3. **FDA Review of Launch Advertising**: We propose to submit to the FDA advertising concepts for MEVACOR™ Daily prior to product launch.
4. **Pre-Purchase Consumer Assistance Program**: This will assist consumers with the self-selection process in determining if MEVACOR™ Daily is right for them.
5. **Cholesterol Testing Referral Service**: Merck and GSK commit to providing consumers with information on how they can get cholesterol testing and obtain pre-treatment and on-therapy cholesterol test results.
6. **Inside the Package Materials**: These will enhance selection and de-selection of the product, as well as encourage positive therapeutic lifestyle changes in addition to lipid lowering therapy.
7. **Persistence/Compliance Post-Purchase Program**: Merck and GSK commit to developing an interactive, individually tailored persistence/ compliance program that is based upon successful consumer communication programs for other Rx and OTC products.
8. **Healthcare Professional Interaction**: Materials will strongly encourage consumers to ask their doctor or pharmacist if they have any questions about the product. Consumers will also be directed to see their doctor regularly and discuss cholesterol management and their use of MEVACOR™ Daily.
9. **High CHD Risk Consumer Identification and Referral Service**: Merck and GSK commit to messaging that will drive high-risk consumers to their physician for appropriate treatment.
10. **Professional Education Programs**: This will involve health care professionals (with a focus on pharmacists) to raise awareness and knowledge levels about the diagnosis and treatment of hypercholesterolemia.

5.2 In-Market Monitoring

Given the potential for MEVACOR™ Daily to be the first statin to switch to OTC, Merck and GSK commit to develop and implement a comprehensive in-market monitoring program to track consumer usage patterns to identify and report to FDA consumer behavior that may compromise appropriate consumer use. The proposed in-market monitoring program will allow for an accurate picture of actual usage information including self-selection, usage patterns, and de-selection. If necessary, adjustments will be made to the MEVACOR™ Daily Self-Management System to improve consumer safety and benefit. For more detailed information see Section C, MEVACOR™ Daily Self-Management System and Marketing Plans.

In summary, our goal is to ensure efficacy, safety, and appropriate consumer behavior with MEVACOR™ Daily.

6. Benefit/Risk Assessment of Nonprescription Lovastatin

6.1 Benefit/Risk Overall Summary

MEVACOR™ Daily is intended for use as primary prevention of CHD by consumers who are at moderately high risk of CHD, consistent with the NCEP ATP III Guidelines (see Appendix 5). The importance of primary prevention of CHD is well-established and the value of statins, including lovastatin 20 mg, for decreasing cardiac events in this population is accepted. Additionally, persons who are at lower NCEP ATP III risk can still be at significant risk of CHD, and treatment with lovastatin has been shown to decrease CHD events in these individuals. The label criteria endorsed by the Advisory Committee and FDA in 2005 are consistent with these Guidelines. However, Framingham 10-year risk scores for people meeting these criteria may suggest 10-year risk less than 5%, especially in women less than 65 years old.

A significant gap currently exists in both the identification and treatment of individuals with elevated cholesterol. MEVACOR™ Daily would help narrow this gap because of:

- Interest by consumers and acceptance by health care providers of increased self-care options.
- A marketing and support campaign designed to increase consumer awareness and appropriate lipid management, including life-style and prescription drug approaches.
- Evidence that therapeutic lifestyle changes will be maintained or improved with the availability of MEVACOR™ Daily.

The availability of MEVACOR™ Daily is expected to increase appropriate consumer interaction with health care providers (as evidenced in CUSTOM), which will also result in consumers being initiated by their physicians on therapeutic lifestyle changes or, when appropriate, on prescription statins.

The potential risks with use of this product have been appropriately addressed. Key concerns include the potential for myopathy, use by women of childbearing potential, and use by individuals with undiagnosed hepatic disease. The first two of these, myopathy and use by women of childbearing potential (i.e., potential for fetal exposure), have been effectively addressed by the currently proposed Drug Facts and other package material. The third issue, use with undiagnosed hepatic disease, has been addressed through studies that demonstrated minimal, if any, hepatic risk in these individuals. A more detailed review of the potential benefits and risks of over-the-counter lovastatin is presented below (see Section D, Benefit/Risk Assessment and Conclusions for a full review).

6.2 Benefits

6.2.1 Primary Prevention

The benefit of statin therapy (with therapeutic lifestyle changes) for individuals without CHD or CHD risk equivalents is well established and endorsed by ATP III Guidelines, and there is a strong safety profile for the 20 mg dose of lovastatin. It is notable that the benefit of statin therapy has also been demonstrated for individuals at lower risk. In AFCAPS/TexCAPS 35% of subjects had a 10-year Framingham Risk score of less than 10%. Nevertheless, over the 5 year study period 21% of the cardiac events still occurred in these individuals [4]. In this sub-group, treatment with lovastatin reduced the relative risk of a cardiac event by 34% (95% confidence interval -9% to 60%, p=0.10). This did

not reach statistical significance, likely due to sample size limitations, but the estimated effect size is consistent with that seen in the overall study population. Benefit of statin treatment in lower risk populations is consistent with the concept that relative risk reduction with statin therapy is largely independent of the pre-treatment absolute risk.

With regards to life-time prevention, the ATP III Guidelines acknowledge that the 10-year risk estimates are less reliable for selecting candidates for medical therapy. The lifetime risk of CHD continues to be significant in the United States with a 1 in 2 risk for men and a 1 in 3 risk for women who are free of CHD at age 40 years. Consequently, the ATP III Guidelines support earlier treatment of individuals with LDL-C levels of 160-189 mg/dL even when the 10 year risk is less than 10%.

In summary, the importance of primary prevention of CHD is well-established, and the value of statin therapy is accepted. In addition, the benefit of statin therapy in lower risk individuals has also been demonstrated and acknowledged. Thus, as agreed in 2005, the proposed label criteria continue to target a population which merits treatment and can obtain the benefit of CHD risk reduction.

6.2.2 Treatment Gap

A significant number of persons in the United States are unaware that they have elevated cholesterol. Furthermore, many persons who do know that they have a cholesterol problem are untreated. Finally, among those who are being treated, a significant proportion is not achieving target cholesterol levels. The scope of these problems is demonstrated by two epidemiologic studies summarized below.

- The 1999 to 2000 National Health and Nutrition Examination Survey (NHANES) evaluated men and women aged ≥20 years who were a representative sample of the non-institutionalized civilian US population [5]. Survey participants with hypercholesterolemia were identified (total cholesterol concentration ≥200 mg/dL or use of a cholesterol lowering medication). There were a total of 4,148 such participants of whom 35% were aware of this condition. The proportion of these hypercholesterolemic participants who were being treated (with medications) was 12.0%, and the proportion whose hypercholesterolemia was controlled (total cholesterol <200 mg/dL) was only 5.4% (7.5% of men and 3.7% of women).
- The Minnesota Heart Survey is an ongoing population-based surveillance of trends in cardiovascular disease risk factors, morbidity, and mortality. It consists of independent, cross-sectional samples of adults (aged 25-74 years for the 1980 to 1982 survey, and aged 25-84 for subsequent surveys) from the Minneapolis-St Paul, Minnesota metropolitan area [6]. Hypercholesterolemia was defined as a total cholesterol concentration ≥200 mg/dL or use of a cholesterol lowering medication. Results from the 2000 to 2002 survey (of 1,352 participants) found that the age-adjusted prevalence of hypercholesterolemia was 54.9% for men and 46.5% for women. Only approximately 46% of hypercholesterolemic participants were aware of their condition. Only 19% of men and 12% of women were aware of and treating their hypercholesterolemia (with medications) and even smaller proportions

were treating it successfully (defined as a total cholesterol concentration <200 mg/dL): 13.1 % of men and 6.0% of women.

Both studies identified very significant awareness gaps of over 50%. Among those who were aware of their hypercholesterolemia there were even larger treatment gaps: about two-thirds of those in NHANES and about 60% of men and 75% of women in the Minnesota Health Survey who were aware of their hypercholesterolemia were not being treated with medications. Of those being treated, significant proportions were achieving only partial success.

6.2.3 Narrowing the Treatment Gap with MEVACOR™ Daily

6.2.3.1 Responsible Promotion of MEVACOR™ Daily is anticipated to increase consumer awareness and treatment of elevated cholesterol

The goal of the promotion campaign for MEVACOR™ Daily will be consumer education and encouragement of greater participation in their health care. Thus, the campaign will emphasize the benefits of lowering cholesterol, the importance of knowing one's cholesterol values, and the appropriate criteria for self-selection and de-selection for MEVACOR™ Daily, emphasizing that the product is not right for everyone. Similar consumer education and participation campaigns in other areas of public health risk, such as smoking, hypertension, and breast cancer screening have resulted in improvements in consumer behavior (see Appendix 7). In the nonprescription environment similar beneficial results have been achieved with smoking cessation, low dose aspirin and, most recently, obesity. The MEVACOR™ Daily in-package materials, and internet- and telephone-based assistance programs will further enhance awareness and education among interested consumers beyond that achieved in the broader community by advertising alone. A further advantage will occur through greater ease of access since physician and pharmacist interaction will not be required with the same rigor as for prescription statins.

6.2.3.2 Consumers' diet and level of exercise will be maintained or improved with the availability of an OTC statin

Exercise and an appropriate diet are cornerstones of lipid management of hyperlipidemia. These should always be recommended and, with the exception of higher risk patients, are initiated prior to consideration of cholesterol lowering medications. Even when medications are indicated, proper diet and exercise are expected to continue.

Concern has been expressed that the availability of OTC statins might lead individuals to disregard these lifestyle habits [13; 14]. In fact, there is evidence to suggest that the opposite would happen. Results from surveys of consumers interested in using an OTC statin have shown that these are persons who describe themselves as being informed on health prevention issues and are already engaged in appropriate lifestyle activities. A large majority reported getting health information from health care providers (72%) or from the internet (65% to 74%). Forty-four percent reported exercising or maintaining a healthy weight and 42% to 45% reported watching their diet or choosing low fat options.

Thus, the evidence supports that these are informed individuals who are currently actively engaged in maintaining their health.

Would these people abandon their lifestyle efforts with the appearance of an OTC statin? Results from CUSTOM indicate otherwise. Self-reported dietary habits were maintained or improved in 98% of users of lovastatin OTC. The participants also completed a dietary assessment questionnaire and by the end of the study, 27% of them had improved their diets. Self-reported exercise habits were maintained or improved in 94% of the participants. Thus, the evidence supports that the availability of an OTC statin and the associated support system will reinforce the importance of lifestyle management to the consumers who are interested in this treatment option.

6.2.3.3 Published estimate of the impact of an OTC Statin on CHD prevention in the US Population

A newly published (Oct-2007) study used population impact measures to estimate the impact on CHD events if MEVACOR™ Daily was available (see Appendix 10). Data from the National Health and Nutrition Examination Survey III were used to provide the numbers of Americans at risk of CHD in each of three different risk categories. These categories were based on the ATP III risk score and were low (<10% risk), moderate (10-20% risk) and high (>20% risk). The 37% decrease in risk of a first major coronary event that was seen in AFCAPS was used as the effectiveness of nonprescription lovastatin for the low to moderate groups. This was compared to a 16% risk reduction due to therapeutic lifestyle changes for the low to moderate risk groups.

Therapeutic lifestyle changes prevented more CHD events than MEVACOR™ Daily due to greater proportions of the population initiating and persisting with lifestyle changes than with MEVACOR™ Daily. Nonetheless, based on the assumptions taken, the analysis demonstrated that the availability of MEVACOR™ Daily would prevent over 500,000 CHD events in the low and moderate risk populations over a 5 year period.

Dr. Eric Brass et al. (see Appendix 9) performed an analysis using the CUSTOM data, applying more conservative assumptions, and reached a similar qualitative conclusion regarding the public health benefit of nonprescription lovastatin.

6.2.4 Benefit Summary

It has been estimated that there are 23 million Americans without CHD or CHD equivalents who have a 10-year Framingham Risk Score of 10-20% [15]. Based on the results of NHANES and the Minnesota Heart Survey, half or more of these people are untreated. Surveys have found that there is interest among patients and support among physicians and pharmacists for an OTC statin. There is evidence that persistence and compliance with an OTC statin would be similar to that for prescription statins and that consumers' diet and exercise patterns would be maintained or improved. Thus, the availability of an OTC statin clearly has the potential to help narrow the treatment gap. In fact, a study using population impact measures determined that the availability of MEVACOR™ Daily would prevent over 500,000 CHD events in a 5-year period.

6.3 Optimizing the Target Population

Following the 2005 Advisory Committee hearing, FDA identified areas of focus to reduce inappropriate use. These were:

- use by women younger than 55 years of age;
- use by persons with lower risk of CHD;

The concern regarding use by women younger than 55 years of age is based on two issues: a relatively low risk of CHD, and the possibility of use while still of childbearing potential. This concern will therefore be addressed under those two categories.

The MEVACOR™ Daily labeling and the Education and Support System are intended to minimize use by people with lower CHD risk. However, some use by lower risk consumers will be inevitable. Persons who have a low Framingham Risk Score can still be at risk of a cardiac event in the short term. This was shown in a study of 222 adults (mean age 50 years) who presented with an acute myocardial infarction [26]. Seventy percent of those individuals had a Framingham Risk Score of less than 10%.

Evidence is accumulating that the Framingham Risk Score may not accurately predict risk of cardiovascular disease in all patients, including in those with two or more known major risk factors. This appears to be particularly true for women for whom, even up to the age of 80 years, more than three-quarters have a 10-year Framingham Risk Score below 10% [16]. This despite the fact that cardiovascular disease is the leading cause of death among women in the United States [17] and is responsible for more deaths in women than all forms of cancer combined [18]. In fact, the lifetime risk of CHD after age 40 years has been estimated at 32% for women (and 49% for men) [16].

The 20-25% LDL-C reduction seen with lovastatin remains an important benefit, and persons with low Framingham Risk Scores, especially women, can still be at risk of a cardiac event and could benefit from lipid lowering therapy. A post-hoc analysis of AFCAPS/TexCAPS data showed that treatment of the lower risk study patients with lovastatin decreased the relative risk of a cardiac event by 34%.

6.4 Potential Safety Concerns

6.4.1 Inappropriate use in the presence of muscle symptoms and with interacting medications

Large, long-term placebo-controlled clinical trials have demonstrated that myopathy with lovastatin 20 mg occurred rarely and its frequency was not increased when used with potent CYP3A4 inhibitors. The proposed labeling for MEVACOR Daily includes warning information on potential muscle symptoms and information on potential interacting medications. As noted previously in Section 2 of this Overview, this labeling includes revisions designed to improve compliance with the muscle warning. The label comprehension studies that are summarized in this background document demonstrated that consumers clearly understood what actions to take if they developed symptoms consistent with myopathy. Furthermore, they clearly understood what actions to take in the event of concomitant use of medications which would increase the risk of myopathy.

6.4.2 Use by persons with undiagnosed liver disease

The 2005 Advisory Committee voted unanimously that liver function testing is not required for MEVACOR™ Daily. In April 2005 FDA approved new labeling for prescription MEVACOR™, removing the recommendation for liver function testing for doses under 40 mg. However, FDA subsequently requested additional data about the hepatic risk of lovastatin in patients with undiagnosed liver disease. Results from three studies not previously available are briefly summarized below, supporting the conclusion that there is very low risk of hepatotoxicity in patients with asymptomatic liver disease (for more details see Section D., Benefit/Risk Assessment and Conclusions).

A retrospective cohort database study sponsored by Merck was conducted to evaluate patients with pre-existing liver disease who were treated with lovastatin. There was no evidence that lovastatin use was associated with adverse hepatic outcomes. In fact, lovastatin use was associated with substantial and statistically significant decreases in all of the pre-defined study outcomes (incidence rate ratio for Hy's Law: 0.28 [95% CI 0.12-0.55], and for combined secondary outcomes [liver injury or cirrhosis/liver failure]: 0.48 [95% CI 0.42-0.55]).

Another retrospective database study evaluated the use of lovastatin by patients with elevated baseline liver enzymes [19]. There were 3 cohorts of patients: cohort 1 had elevated enzymes and received lovastatin; cohort 2 did not have elevated enzymes and received lovastatin; and cohort 3 had elevated enzymes and did not receive lovastatin. The mean duration and dose of lovastatin was very similar between cohorts 1 and 2 (396 vs. 472 days; and 23 vs. 24 mg/day). After 12 months of follow-up, patients in cohort 1 had comparable mild-moderate enzyme elevations vs. patients in cohort 3 (6.6% vs. 11%, $p=0.2$)) but significantly fewer severe elevations (0% vs. 5.5%, $p<0.01$). Patients in cohort 1 had a higher incidence of mild-moderate enzyme elevations vs. patients in cohort 2 (6.6% vs. 3% $p=0.03$) but not of severe elevations (0% vs. 0.3%, $p=0.9$). No one in cohorts 1 or 2 developed a case meeting Hy's Law whereas 3.5% of patients in cohort 3 did ($p<0.01$ vs. cohort 2, and $p=0.03$ vs. cohort 1). These results showed that patients with elevated baseline liver enzymes were not at a higher risk of hepatotoxicity from lovastatin than patients with normal enzymes.

Finally, a third publication evaluated statin use in subjects with hepatic steatosis (non-alcoholic fatty liver disease) who were enrolled in the Dallas Heart Study [20]. Study results showed that statin use was not associated with a greater prevalence of hepatic steatosis or elevated serum alanine transaminase (ALT), or with an increased prevalence of elevated ALT levels in subjects with hepatic steatosis.

In summary, these large studies clearly demonstrated that the risk of hepatotoxicity with lovastatin use is minimal in patients with pre-existing liver disease. This information reassures that consumers who have undiagnosed asymptomatic liver disease will be at low risk for adverse hepatic events due to use of MEVACOR™ Daily. For those consumers with diagnosed liver disease, the proposed Drug Facts for MEVACOR™ Daily includes a warning to 'ask a doctor before use if you…have liver disease'.

6.4.3 Use by pregnant or nursing women, or women of childbearing potential

Following the 2005 Advisory Committee hearing, the FDA acknowledged any fetal risk from lovastatin is possibly theoretical and probably small, and required that a revised nonprescription label be developed and tested in comprehension and self-selection studies to further minimize any potential risk. In response Merck has revised the Drug Facts portion of the carton label by expanding the pregnancy-related language to include women of childbearing potential. The potential consequences of lovastatin use during pregnancy have also been added. Thus, the pregnancy related language has been expanded from "Do NOT use if you are pregnant or breast-feeding" to "If pregnant or breast-feeding, or think you may become pregnant, do not use. This product may cause problems in the unborn child". Potential use by pregnant or nursing women or women of child-bearing potential was evaluated in the SELECT Study. In SELECT four pregnant women, one nursing woman, and 21 women who said that they may become pregnant evaluated the package for MEVACOR™ Daily. All 26 women made the appropriate decision to not purchase the product. These results are consistent with those seen in the CUSTOM study in which all 12 pregnant women who evaluated lovastatin OTC decided not to purchase.

Women of child-bearing potential can be defined as women who have not yet reached menopause. The age of natural menopause in the United States, as evaluated in two cohort studies [21; 22], was determined to be 51 years. The probability of being menopausal increased rapidly thereafter and was greater than 80% by age 55 years.

The results from SELECT demonstrated that the current labeling was largely effective in limiting use to women in the appropriate age range (55+ years). As just noted, the vast majority of women in this age range are menopausal. Of the women in SELECT who were younger than 54 years and who chose to purchase the product, 38/48 or 79% were 45 to 53 years of age. This is an age range when natural fertility has decreased to very low levels or when, in many cases, menopause has been reached. Thus, the risk of inadvertent exposure to MEVACOR™ Daily during pregnancy can be expected to be very low. As acknowledged by the FDA and supported by the review of current information (summarized in Section D., Benefit/Risk Assessment and Conclusions), the risk of fetal toxicity is small and may be theoretical. Thus, the proposed labeling for MEVACOR™ Daily adequately minimizes fetal risk. The data clearly establish that the fetal risk from MEVACOR™ Daily is very small, and that the label will result in OTC consumers using MEVACOR™ Daily very rarely while pregnant. Thus, any public health risk is exceedingly low and is offset by the drug's benefits.

6.5 Benefit/Risk Conclusion

Following the 2005 Advisory Committee deliberations, the FDA outlined the residual issues which needed resolution prior to approval for MEVACOR™ Daily. These centered around the consumers' ability to appropriately self-select for use of the product based on label information. In response, the product labeling and in-package materials were accordingly revised tested. The final proposed materials were evaluated in representative and low literate populations in two consumer comprehension studies. The

Pivotal Label Comprehension Study #087 demonstrated effective communication of the key usage directions, warnings, and cautions on the package label. The Muscle Warning Comprehension Study #088 demonstrated excellent comprehension of warning language regarding unexplained muscle pain, tenderness or weakness.

The self-selection study (SELECT #086) showed meaningful improvement over CUSTOM in appropriate self-selection in women <55 years of age and in women of childbearing potential. However, the SELECT results were similar to those of CUSTOM for its third goal of minimizing purchase by low CHD risk individuals, despite the marked decrease in intent to purchase by women under the age of 55. In both CUSTOM and SELECT, women made up a disproportionate number of these lower risk individuals. This may be a function of the Framingham Risk Score since, even up to the age of 80 years, more than three-quarters of women have a 10-year Framingham Risk Score of less than 10% [16]. The label criteria, which remain consistent with NCEP Guidelines and were endorsed by the Advisory Committee in 2005, do allow use by consumers of lower CHD risk, as defined by the Framingham Risk Score. However, there is substantial evidence, which has led to updated AHA Guidelines for women, that women at lower CHD risk can benefit from lipid lowering therapy, and the overall benefit/risk relationship remains very favorable.

The potential benefits and risks of over-the-counter lovastatin have been carefully reviewed. The potential risks of myopathy and fetal exposure have been demonstrated to be appropriately minimized based on the results of the label comprehension and self-selection studies. Additionally, studies have demonstrated that there is minimal hepatic risk with the use of MEVACOR™ Daily by consumers with undiagnosed liver disease. An effective OTC treatment option for elevated cholesterol is anticipated to narrow the treatment gap and to decrease the number of cardiac events on a population basis. The MEVACOR™ Daily Self-Management System which will be in place post-approval will help ensure appropriate use of the product by consumers, and will drive awareness and education about CHD prevention. In summary, the potential risks of over-the-counter lovastatin have been appropriately minimized and the opportunity for benefit supports approval of non-prescription access to lovastatin 20 mg.

B. CONSUMER BEHAVIOR

B. CONSUMER BEHAVIOR

1. Background

1.1 History

The original New Drug Application (NDA) for nonprescription lovastatin 10 mg was submitted to the United States Food and Drug Administration (FDA) in 1999. The purpose of the application was to provide information and a compelling case supporting the suitability of lovastatin 10 mg for nonprescription use to lower cholesterol in a moderate cardiovascular risk population. 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.

As a result of numerous communications and input from FDA and the issuance of the NCEP ATP III Guidelines (see Appendix 5), the proposed daily dose of nonprescription lovastatin was changed from 10 mg to 20 mg, and the OTC treatment paradigm, product labeling, and consumer support materials were significantly evolved from the original NDA. Additional consumer behavior data, most notably from the CUSTOM actual use study (A **C**onsumer **U**se **St**udy of **O**TC **M**EVACOR™) were generated to support approval of this application, and these data were submitted to FDA in 2004.

During the January 13-14, 2005 joint FDA Advisory Committee deliberations, a number of the long-standing issues relating to safety and benefit of lovastatin 20 mg were satisfactorily addressed, as evidenced by the highly positive Committee votes on those topics. Nonetheless, the majority of the Committee members voted against approval for OTC availability due to concerns related to appropriate consumer self-selection behavior.

The issues identified in the subsequent NDA Action Letter centered around consumers' ability to appropriately self-select for use of the product based on label information. There was particular interest in improving messaging in the areas of use by women less than 55 years, women of childbearing potential, low coronary heart disease (CHD) risk consumers, and those who experience muscle toxicity. As a result, the primary focus of this background information document is on the results of the self-selection study titled **S**elf **E**valuation of **L**ovastatin to **E**nhance **C**holesterol **T**reatment (SELECT), and two label comprehension studies which were conducted to address these specific issues. Dr. Eric Brass, who participated in the design and evaluation of the SELECT study, has co-authored a manuscript, and a complete pre-publication draft is included at the end of this section (see 3. SELECT Study Manuscript Submitted for Publication)

Although the main focus of this background information is on the above-referenced studies, the consumer behavior data from the previous studies remain informative and valid and provide support for nonprescription availability of lovastatin. Where appropriate, these data will be summarized in this section on consumer behavior.

1.2 Revisions to Product Labeling

The product labeling has continued to evolve from the original NDA to the present in response to input from FDA Advisory Committee meetings, the FDA, and accrued data. The current proposed LDL-Cholesterol (LDL-C) paradigm carton label was designed to improve clarity versus the previous label tested in the CUSTOM Study while retaining the most critical coronary heart disease (CHD) risk assessment factors in NCEP ATP III guidelines. It focuses on warnings regarding key contraindications, simplified eligibility criteria, and enhanced explanation of likelihood of individual benefit. As suggested by the FDA, this revised label was tested in label comprehension studies and the SELECT study. The full label text of the SELECT LDL-C label is included in Appendix 4.

Alternative Total-Cholesterol Label Paradigm

In an effort to simplify the Eligibility Criteria section of the MEVACOR™ Daily product label, increase the ability of consumers to appropriately self-select, and maintain overall consistency with NCEP ATP III, Merck developed a Total Cholesterol (Total-C) product label in which the LDL-C 130-170 mg/dL criteria was replaced with the well-known "borderline elevated" Total-C range of 200-240 mg/dL. In addition, the eligibility criteria for men were simplified to include only age and Total-C range. Total Cholesterol (Total-C) is one of the five factors used in the ATP III Framingham risk assessment, and it also has potential utility as many consumers are familiar with it and can relate to the value when determining if the product is right for them. Major AHA and NHLBI consumer initiatives focus on Total-C awareness, and numerous direct-to-consumer advertisements for heart healthy foods and prescription statins use total cholesterol to communicate to consumers who may be eligible for therapy.

In order to ensure that the self-selection paradigm for MEVACOR™ Daily has been optimized, the label comprehension and SELECT studies included a direct comparison of labels based on LDL-C and Total-C. The full text of the SELECT Total-C label is included in Appendix 4.

Unexplained Muscle Pain Warning

At the January 2005 Advisory Committee meeting, Committee members unanimously agreed that the low risk of muscle toxicity with lovastatin 20 mg was acceptable for an OTC drug. However, FDA requested that labeling changes be made in order to improve compliance with the muscle warning during ongoing use. Label comprehension testing was recommended to document the improvement in the labeling. As a result, the MEVACOR™ Daily inner package materials (Quick Start Guide and Package Insert) were modified to strengthen the communication of the warning about unexplained muscle pain during product use. Also, a "refrigerator magnet" was developed to repeat the muscle warning text and serve as an added reminder for consumers. The magnet will be included with the other internal package materials for MEVACOR™ Daily. All of these materials contain a more thorough explanation of the condition and possible consequences of not heeding the warning. These revisions were tested in Muscle Warning Comprehension Study #088, the results of which are described later in this

section, and clearly show that consumers understood what they should do if they developed such symptoms.

Women of Childbearing Potential

During the January 2005 Advisory Committee meeting, most Committee members agreed that lovastatin was not so potentially toxic to the fetus to prevent its marketing OTC under any circumstance; however, Committee members agreed that the then-proposed OTC label needed to be more directive about potential use in pregnancy. As a result, the proposed Drug Facts label language for MEVACOR™ Daily has been revised to enhance comprehension of the warning against use in women of childbearing potential. The following language was added to increase the impact of the message: "**If pregnant or breast-feeding, or think you may become pregnant**, do not use. This product may cause problems in the unborn child." This language is now consistent with language in direct-to-consumer advertising for prescription statins. The front of the box was also modified so that the appropriate age requirements are prominently displayed. These modifications of the label were tested in label comprehension studies and in SELECT. The results, described later in this section, demonstrated that the current labeling was very effective in communicating this message.

2. Consumer Behavior Data

In order for lovastatin 20 mg to be considered suitable for nonprescription status, the following criteria are examined in consumer behavior studies:

- Consumers should demonstrate sufficient comprehension of the product label text 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

The essential element in meeting the criteria for approvability of nonprescription lovastatin is the effectiveness of the product package label in generating appropriate consumer behavior. The label has evolved with the clinical development program from its inception in 1997. Table B-1 provides summary descriptions of the consumer behavior studies that comprise the clinical development program for nonprescription lovastatin.

Table B-1
All Open-Label Consumer Behavior Studies for Nonprescription Lovastatin

Protocol Number	Short Study Name/Study Description/Setting	Design	Treatment Duration	Visited Study Site (N)	Took Study Drug (N)
Lovastatin 20 mg (Amended 2007 NDA Resubmission)					
086	**SELECT Study**: Consumer behavior study of self-assessment and purchase decisions in a storefront setting	Open label Non-comparative All-comers (minimal exclusions) Self-assessment and purchase intent No drug dispensed	None (non-drug study)	1528	431[†]
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	3346	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)	6095	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	1312	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	2416	1144

[†] Although no drug was actually provided in SELECT, 431 participants indicated their intent to purchase MEVACOR™ Daily before being told that they could not have access to drug.

The consumer behavior data summarized in this section of the Background Information Package are identified in Table B-2. As previously mentioned, following the 2005 Advisory Committee meeting, FDA identified two areas where improvement in consumer behavior was necessary: initial self-selection, and the ongoing use decision regarding development of unexplained muscle pain. It was suggested that the product labeling be revised and tested in label comprehension and self-selection/use studies. Therefore, the focus of the current joint Advisory Committee meeting is on label comprehension of the

revised product materials and improvement of self-selection behavior. The other ongoing use consumer behavior data (e.g., follow-up cholesterol test, deselection, compliance and persistence) from the CUSTOM Study were deemed acceptable by the FDA. However, these data remain valid and relevant, and are summarized here to provide a complete picture of the consumer behavior data supporting nonprescription availability of lovastatin 20 mg.

Table B-2
Nonprescription Lovastatin Consumer Behavior Study Data

Study	OTC Drug Distribution Paradigm	Use Decisions		Cholesterol Knowledge‖	Compliance/ Persistence
		Self-Selection‡	Continued Use§		
Lovastatin 20 mg (Amended 2007 NDA Resubmission)					
SELECT Study (Protocol 086)	Open shelf	✓		✓	
Lovastatin 20 mg (Amended 2004 NDA Resubmission)					
CUSTOM Study (Protocol 084)	Open shelf	✓	✓	✓	✓ (6 months)
Lovastatin 10 mg (Original NDA Submission)					
Pharmacy Study (Protocol 076)	Open shelf	✓		✓	✓ (18 months)
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.
‡ Self-selection in SELECT included self-assessment and purchase decisions. Self-selection in CUSTOM was purchase decision only (there was no self-assessment component)
§ 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.

The new studies conducted since 2005 are summarized in this section and are organized as follows:

- Pivotal Label Comprehension Study #087
- Muscle Warning Comprehension Study #088
- Self-Selection in SELECT Study #086

Additionally, ongoing use data from prior studies will be summarized.

2.1 Pivotal Label Comprehension Study #087

The Pivotal Label Comprehension (PLC) Study measured consumer comprehension of the messages on the carton and Drug Facts label of the MEVACOR™ Daily package. It was a two-cell study, testing two different usage paradigms based on LDL-C and Total-C. The labels that were tested had evolved from revisions made based on iterative consumer testing as well as FDA input on the usage paradigm and the label's content and format.

2.1.1 Objectives

- The primary objective was to measure consumer comprehension of the following communication messages on the label:
  - What the product is and what it is used for;
  - Criteria for use (diet and exercise, cholesterol numbers from fasting test, age/gender);
  - Warnings and cautions (Do not use, Ask a doctor before use, Ask a doctor or pharmacist before use);
  - When using product: what to do if change in health or unexplained muscle pain; and
  - Directions for use (who could use, dose, goal messages).
- A secondary objective was to test comprehension of two different usage paradigms based on LDL-C and Total-C; therefore, the study included two cells that were identical in all elements apart from their focus on the two different types of cholesterol.

Finally, the results were evaluated among both a general representative sample of adults and low health literacy adults.

2.1.2 Study Design

This two-cell study was conducted in 20 geographically and demographically dispersed malls. There were 610 respondents in the combined total representative sample (of which 109 were of low health literacy), which was then augmented to reach a total of 315 low health literacy respondents. Participants were screened to be cholesterol-concerned and neutral to positive on the general concept of an OTC cholesterol-lowering product called MEVACOR™ Daily. They were randomly assigned to the two cells. They then reviewed the package label and answered comprehension questions.

Because the goal of the study was not just to measure but also to understand comprehension, the questions were designed to understand the thought process behind the decisions respondents made. Therefore, most of the questions were in "scenario" format, describing hypothetical people with specific characteristics that caused them to be appropriate or not appropriate to use the product. Most of the scenario questions were asked in two parts: Do you think it is okay or not okay for the hypothetical person to use the product, and why did you give that response? Together, these two questions were inputs into an analysis that classified responses as "correct", "acceptable", or "incorrect"

based on a pre-defined code structure. This methodology was developed with FDA input on the MEVACOR™ Daily draft label, the comprehension protocol and the questionnaire.

While the data tables show the correct, acceptable, and incorrect scores separately, they also show a combined "correct plus acceptable" score, and much of the discussion focuses on these C+A data. The inclusion of "acceptable" acknowledges the reality that consumers can have their own well-thought-out reasons for decisions that may not be completely consistent with the label information but are understandable and appropriate for them. In fact, in most cases in this study, the level of "acceptable" responses was low; most of the responses could be classified as "correct" or "incorrect."

Classification of low health literacy was accomplished using a brief literacy test known as the Rapid Estimate of Adult Literacy in Medicine (REALM). The REALM test is a reading exercise that is used to assess respondents' familiarity with medical terms. Missing a pre-defined number of words on a list corresponds to an 8th grade reading level or lower. This test is frequently used by sponsors and FDA to define a low health literacy subgroup.

2.1.3 Results

2.1.3.1 Overall Performance on Study Objectives

The goal of this study was to measure and also to understand consumer comprehension of the communication messages on the package label. To this end, most of the questions were designed to elicit the thought processes that led to respondent decisions about when the usage of MEVACOR™ Daily is and is not appropriate. Therefore, the results are primarily based on data from both the "okay/not okay" decisions and the follow-up verbatim reasons for the decisions. As predefined, the results presented are primarily the correct + acceptable (C+A) scores. In the great majority of cases, the "acceptable" portion of the C+A score was small.

Total Combined Representative Sample

The total combined representative sample of 610 respondents demonstrated a solid understanding of the great majority of these messages, particularly the key safety warning and caution messages. Of the 31 scenario questions, the total representative sample achieved scores of 80% or higher C+A on 26 questions, and 90% or higher C+A on 19. Scores of 96% or higher were reached on the three contraindications of pregnancy, allergy and breast-feeding. Additionally, these respondents achieved C+A scores of 86% or higher on 11 of the 12 scenarios addressing medications and medical conditions, including several "false positive" scenarios. It is also important to note that respondents attained very strong scores, generally over 90%, on questions about product use and directions. The treatment to goal message scores yielded mixed results, with several reaching 85% or higher and several under 70%. Eighty-five percent of the representative sample knew that a product user should get a cholesterol test after starting to use the product, and 92% understood that cholesterol would or could go back up if a user stops using the product. However, just 61% correctly answered that the follow-up test should

take place at six weeks, and 69% understood that if the treatment goal is not reached, a person should talk with a doctor.

The five scenarios that scored lower than 80% were benefit-related, and three of them focused on cholesterol levels. The other two addressed the heart disease risk factor and one of the goal messages. The lowest scores were 45% for the heart disease risk factor (addressed later in this document), 69% for what to do if you don't reach a healthy level after using, 71% for too-high HDL, 73% for too-high LDL, and 79% for LDL/Total-C in the appropriate range.

LDL-C versus Total-C Usage Paradigms

The second objective of this study was to test two different self-selection paradigms based on LDL-C or Total-C. Very few significant differences emerged between the two paradigms for the common label elements, but the Total-C group scored significantly higher on three scenarios related to cholesterol values: LDL-C/Total-C in the appropriate range, LDL-C/Total-C lower than the appropriate range, and HDL higher than the appropriate range. The first two are probably a result of the fact that total cholesterol is a more widely understood measure among consumers than LDL-C. The reason for the difference in scores for high HDL is likely due to the extra mention on the back flap of the Total-C package.

Low Health Literacy Subgroup

The final major objective of this study was to evaluate the results among both the general population of adults and adults with low health literacy. The total combined low health literacy subgroup, with a sample size of 315, scored 80% or higher C+A on 23 of the 31 scenarios and 90% or higher on 14. Scores of 92% or higher were achieved on the three absolute contraindications, with pregnancy and breast-feeding reaching 96%. They also scored over 80% on nearly all of the remaining precautions. The lower scoring scenarios were generally consistent with those for the representative sample. The lowest scores were 33% for the heart disease risk factor (addressed later in this document), 63% for what to do if you don't reach a healthy level after using, 70% for too-high LDL, and 71% for too-high HDL.

Similar to previous studies, the low health literacy subgroup generally scored somewhat below the level attained by the non-low health literacy subgroup. However, it is important that the low health literacy subgroup scored well in the most important safety messages.

2.1.3.2 Specific Label Message Segments

Use and Directions

Total representative and low literate respondents demonstrated a high level of understanding regarding what MEVACOR™ Daily is used to treat, frequency of use, and dosage; all of these scores were over 90%. Scores for the best time to take the product reached 80% among the representative sample and 70% among the low health literacy subgroup.

Pre-Use Messages

The total representative sample understood the behaviors that precede product usage: fasting before getting a cholesterol test (90%), having a recent test (88%), improving eating patterns (93%) and trying diet and exercise first (83%). The low health literacy subgroup C+A scores on these questions ranged from 90% (improving eating patterns) to 73% (having a recent test).

Usage Criteria

These scenarios fell into three fairly distinct groupings for the total representative sample: very high scores around 90% or higher, somewhat lower scores from 73% to 83%, and one score that was extremely low. The highest scores demonstrated that respondents understood the messages regarding the appropriate male and female ages to use the product and that potential product users must know their cholesterol numbers first. The second group of scores included those that explored specific cholesterol values that were within the appropriate range or were too high or too low. As noted earlier, for several of these scenarios, the Total-C cell achieved significantly higher scores than the LDL-C cell.

Finally, the scenario that described a woman with a family history of heart disease had the lowest score in the study (45% C+A among the representative sample, and 33% C+A for the low health literacy subgroup). It is likely to have been due to a combination of factors, but is important to note that respondents erred on the side of safety, as they said that it was not okay for this person to use the product when, in fact, it was okay.

Warnings and Precautions

As noted earlier, the three most important safety warnings describing pregnancy, breast-feeding and allergy to lovastatin were well understood by both the total representative sample and the low health literacy subgroup, as demonstrated by C+A scores that, with one exception, exceeded 95%. The one exception was the allergy score among the low literate subgroup, which was 92%.

Both the representative sample and the low health literacy subgroup scored 71% C+A for the high HDL scenario. HDL is a relatively unfamiliar concept to some respondents and may be difficult to communicate in the context of the main message on the package, which focuses on the importance of lowering LDL or Total cholesterol. Given these factors, the C+A score of 71% for HDL is a reasonable result.

The rest of the medication and medical condition messages achieved scores among the representative sample in the high 80% and 90% ranges. The highest scores for pre-use cautions were seen for liver disease (96% C+A), diabetes (95%), using a prescription oral antifungal medicine (94%) and concurrent use of a prescription cholesterol medicine (92%). Over-time use cautions were also well understood, with the muscle pain warning reaching 97% C+A and developing kidney disease (as an example of a change in medical condition) scoring 92% C+A among the representative sample. Scores among the low health literacy subgroup for these two key messages were 96% and 93%, respectively.

Post-Use Testing Messages

It is important to note that although scenarios and questions were included to test the over-time use testing and goal messages, the results cannot be fully interpreted without all of the package materials and systems in place, most of which emphasize proper use over time. Additionally, the key areas for label improvement based on FDA guidance after the 2005 Advisory Committee meeting were initial usage decisions, since the over-time behavior in the CUSTOM trial, where participants had access to the extra support program and in-package materials, was considered to be acceptable and did not need to be re-tested in the SELECT trial.

The total representative respondents demonstrated a high level of comprehension for two of these messages: 85% acknowledged that a product user will need to have cholesterol re-tested after starting use and 92% understood that if someone stops using the product, their cholesterol level would (or could) go back up. The low health literacy subgroup scores for these two questions were 78% and 90%, respectively. Respondents were less clear on the timing of the post-use cholesterol test; 61% were able to state the exact correct answer of six weeks.

It is very important to point out that the over-time use goal and testing messages will be reinforced for product users through the internal package materials and many other elements of the MEVACOR™ Daily support program. Post-purchase support programs have been previously tested in the CUSTOM Actual Use Study, which yielded behavior accepted by the FDA for over-time usage behavior among the participants.

2.1.4 Conclusions from the Pivotal Label Comprehension Study

1. The MEVACOR™ Daily package label effectively communicates the key messages. Study respondents were able to demonstrate, via closed-end and open-ended verbatim questioning, that they understood the key usage directions, warnings, and cautions on the label.
2. The most important safety warnings and cautions demonstrated the strongest message communication. Respondents scored in the mid-high 90% range on the absolute safety warnings, the over-time use muscle warning, and the cautions about liver disease and diabetes. All of the other safety cautions about medications and medical conditions achieved scores of 89% or higher. Additionally, respondents scored well on the eligible age for women (93%) and men (94%).
3. Several of the lower-scoring messages addressed benefit issues. Verbatim responses showed that some confusion was evident regarding high HDL. This may be due to the fact that the package strongly emphasizes the importance of lowering cholesterol (LDL or Total), which is the main reason to use the product. Confusion was also apparent in the verbatims from the heart disease risk factor scenario, partly because heart disease is both a risk factor (family history) and a before-use "talk to doctor" caution on the label.
4. The other messages that did not appear to be as well understood were those that addressed use over time. Scores were somewhat low for comprehension of the exact

time to get cholesterol re-tested after starting use and on what users should do next if they do not reach a healthy cholesterol goal after six weeks. These over-time usage messages will be reinforced in the internal package materials and other elements of the MEVACOR™ Daily market support program. They were previously tested in the CUSTOM actual use trial, where participants had access to support materials and demonstrated acceptable behavior consistent with these messages.

5. The LDL-C and the Total-C labels showed a strong consistency in communication of key messages, with most of the few differences favoring the Total-C label. It is not surprising that the two labels performed comparably on nearly all elements, since the information provided was virtually identical, apart from the focus on cholesterol ranges. The stronger scores attained in the Total-C cell on some of the questions related to cholesterol values can be attributed to the greater familiarity that most consumers have with total cholesterol versus LDL cholesterol.
6. While the low health literacy subgroup scored lower than the non-low health literacy subgroup on some measures, these respondents still achieved C+A comprehension scores of 80% or greater on most key messages. This was particularly evident for the absolute safety warnings and the precautions.

2.2 Muscle Warning Comprehension Study #088

The Muscle Warning Comprehension (MWC) study measured consumer comprehension of the warning relating to the possible occurrence of unexplained muscle pain, tenderness or weakness during use of MEVACOR™ Daily. The specific support materials tested in this study included the Quick Start Guide, the Package Insert, and a "refrigerator message magnet" that could serve as an additional reminder for consumers (copies of these items are in Appendix 4). The muscle warning text used in the package materials has been expanded beyond the concise text found in the Drug Facts label, and includes a more thorough explanation of the condition and the possible consequences of not heeding the warning. The study questionnaire was primarily open-ended and included hypothetical scenarios in addition to open-ended questions.

2.2.1 Study Design

This was a one-cell study, utilizing the LDL-C version of the nonprescription lovastatin package, label and internal package materials. This study was conducted in 20 geographically and demographically dispersed malls. There were 316 respondents in the representative sample, which was then augmented to reach a total of 104 low health literacy respondents. Participants were screened to be cholesterol-concerned and neutral to positive on the general concept of an OTC cholesterol-lowering product called MEVACOR™ Daily. They then reviewed the package label and internal materials and answered comprehension questions. Some of the questions were in "scenario" format, and these scenario questions were asked in two parts: Do you think it is okay or not okay for the hypothetical person to use the product, and why did you give that response? This methodology was developed based on FDA comments on a MEVACOR™ Daily label package, and is highly similar to that used in the PLC Study. The outer package was identical to that used in the LDL-C cell of the PLC study.

2.2.2 Results

2.2.2.1 Performance on the Muscle Pain Objective: Key Measures

A number of measures in the study were used to determine the extent of consumer comprehension of this key objective.

First, 95% of the representative sample and 96% of the low health literacy sample responded to an initial question that they knew that there are possible side effects to watch for when taking MEVACOR™ Daily.

A scenario question tested whether respondents would understand that unexplained muscle pain is an important potential side effect of taking MEVACOR™ Daily. Correct/acceptable (C+A) scores for respondents in both the representative sample (98% C+A) and the low health literacy sample (97% C+A) demonstrate clear understanding that if such pain is experienced, the user should stop taking the product.

Later in the questionnaire, when asked what specific symptoms might indicate a side effect, 96% of the representative sample and 93% of the low health literacy sample responded correctly. Nearly all of these respondents mentioned the word "muscle" in their verbatim responses.

The respondents who mentioned muscle or body pain knew that this symptom could occur at any time after one starts using the product, not just right after starting. Ninety-four percent of the representative sample and 93% of the low health literacy sample knew this. They also knew that ignoring these symptoms could have serious consequences, with 82% of the representative sample and 79% of the low literate sample mentioning the correct conditions such as kidney damage and muscle deterioration. This information reflects the effect of the in-package materials which provide greater detail on the potential for muscle pain.

The warning containing this information was considered extremely serious by the respondents. On a five point scale where 5 was "extremely serious" and 1 was "not at all serious", the mean rating for the representative sample was 4.77, while the mean rating for the low health literacy sample was 4.82. Ninety-three percent (93%) of the representative sample and 95% of the low health literacy sample rated this warning either 5 or 4; that is, either extremely serious or the next highest rating.

Finally, the warning was considered so serious that the nearly all of the respondents said they would contact their doctor (95% representative sample, 93% low health literacy sample) if they experienced muscle or body pain or flu-like symptoms.

2.2.2.2 Performance on the Muscle Pain Objective: Other Measures

The respondents in this study reported a high likelihood that they would remember the warning (92% extremely or very likely among the total representative sample and 90% extremely or very likely among the low health literacy sample), and that they would read at least one of the materials contained inside the package (92% extremely or very likely among the total representative sample and 91% extremely or very likely among the low health literacy sample).

Thus, all the questions related to consumer comprehension of the muscle pain warning and its seriousness indicate that the consumers can understand the warning, take it seriously, and would act on it if they were taking the product and experienced the symptoms.

2.2.2.3 Conclusions from Muscle Study

1. The MEVACOR™ Daily label and in-package materials together effectively communicate the warning about unexplained muscle pain. Study respondents were able to demonstrate, via closed-ended and open-ended verbatim questioning:
   - That they understood that unexplained muscle pain is an important symptom of a potentially serious side effect of using the product;
   - That a product user should stop taking the product and contact a doctor if they experience such symptoms;
   - That serious consequences could result from ignoring muscle pain;
   - That these symptoms could appear at any time after someone begins using MEVACOR™ Daily, not just shortly after they begin using it; and
   - That this is an extremely serious warning.
2. Although these data cannot be compared directly to the CUSTOM label, the enhancements to the label and support materials did produce strong scores for these messages, which support the conclusion that purchasers of this product will notice, understand and heed this important warning. It is difficult to directly compare these results to CUSTOM data because they were obtained differently: the CUSTOM Actual Use trial studied actual behavior and the CUSTOM PLC study questions were in closed-ended multiple choice format. However, through the use of scenarios, open-ended questions and probes, the current study enabled respondents to demonstrate that they could not only respond correctly to a broad question about side effects in general but could also understand the essential elements associated with this specific warning, particularly the symptoms and consequences of muscle pain. These strong results can be attributed, at least in part, to the enhancements that were made to the internal materials that reinforced these messages.

2.3 Self-Selection

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 into a healthy lifestyle of diet and exercise if medication is not needed. In addition to the SELECT Study #086, 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 #084, Pharmacy Study #076, and Red Arrow Study #081.

The primary focus of this section of the summary is on data from the SELECT Study since it represents the current treatment paradigm and product labeling. However, data from CUSTOM Protocol 084 will also be presented for comparative purposes where appropriate since the main goals of SELECT were to improve upon the self-selection results of CUSTOM.

2.3.1 SELECT Study #086

2.3.1.1 Rationale

The CUSTOM study demonstrated that participants could appropriately manage their treatment of cholesterol over time, including treatment to an LDL-C goal, compliance and persistence, and decisions relevant to changes in health status (e.g., new prescriptions, new medical conditions). It also showed that participants achieved beneficial lipid lowering with MEVACOR™ Daily comparable to what was seen in clinical trials. However, some self-selection results in CUSTOM did not achieve desired levels. The following were specific areas in CUSTOM where participants did not self-select appropriately in adequate numbers:

- Women < 55 years of age. In CUSTOM, of the women <55 years of age who evaluated the product, 23.5% (161/685) elected to use MEVACOR™, and 37% (161/430) of the female User population were women <55 years of age.
- Women of childbearing potential. Since women <55 years of age who used MEVACOR™ in CUSTOM were not asked if they could become pregnant, it was conservatively assumed that they were capable of conceiving a child. A question regarding childbearing potential was not asked in CUSTOM and there was no warning relevant to this issue on the label; however the label did contain a warning against use in pregnancy. Thus, the potential use by women of childbearing potential requires greater understanding.
- Lower CHD risk users (<5% risk of CHD in 10 years). In CUSTOM, 27.3% (289/1059) of the users were considered to be of lower risk as defined by the Framingham Risk Calculator. While these consumers would likely benefit from MEVACOR™ Daily, and their benefit/risk ratio would be favorable, many would be below the NCEP threshold for primary prevention. Thus, efforts were made to reduce use by this lower risk population.

To improve self-selection in these populations, a new label was developed, evaluated in label comprehension studies, and assessed in the Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT) Study. This study was designed to evaluate participants' ability to make self-assessment decisions and purchase decisions that are consistent with the new label. The study was also designed to provide insight regarding participants' reasoning when making self-assessment and purchase decisions.

Specifically, the main goals of the study were to improve upon the self-selection results of CUSTOM in these three areas:

- Decrease the proportion of women < 55 years of age who chose to buy the product.

- Decrease the proportion of women of childbearing potential who chose to buy the product.
- Decrease the proportion of lower CHD risk consumers who chose to buy the product.

In addition to these three goals, a fourth goal was to maintain the strong safety decision scores achieved with the CUSTOM label in the CUSTOM study.

2.3.1.2 Objectives

- Using label paradigms with either LDL cholesterol or Total cholesterol as an eligibility criterion for use, evaluate participant's ability to make appropriate self-selection and purchase decisions. Participants' self-selection and purchase decisions were compared to their eligibility assessment to determine if they made correct decisions.
- To provide insight regarding participants' reasoning and factors considered when making self-selection and purchase decisions.

2.3.1.3 Study Design

- "All-comers": exclusions only to limit potential behavior bias (similar to CUSTOM)
- Two-arm: randomization to either LDL Cholesterol (LDL-C) label paradigm or Total Cholesterol (Total C) label paradigm, and stratified by gender
- Multi-center: 7 metropolitan areas in the U.S.; 14 store front study sites (similar to CUSTOM)
- Non-drug: participants were shown prototype market image packages with no drug inside; participants did not know they would not receive drug until after all decision data were collected.

Recruiting and study site logistics were designed to be consistent with the CUSTOM Actual Use Study. For both SELECT and CUSTOM, advertising campaigns were developed that were designed to recruit participants by increasing the awareness about the studies through broadcast media (radio and TV) with a central toll-free number to handle inquiries and schedule appointments. The advertising campaigns were designed to appeal to a broad cross section of generally healthy middle-aged men and women who were concerned about high cholesterol. The recruitment messages for SELECT were nearly identical to those used in CUSTOM in order to attract a similar population. A listing of the recruitment advertisement features for the 2 studies is presented in Table B-3.

Table B-3
Recruitment Advertising Features for SELECT and CUSTOM

	SELECT and CUSTOM Study Advertising (Protocols 086, 084)
Age	No age stated
Cholesterol range to be eligible or cholesterol "messages"	• "…concerned about cholesterol • For some people diet and exercise work, but for others, these are not enough • "…it is important to know your 4 cholesterol numbers"
Other medications or conditions	• None
Product purchase requirement	• Not in advertising. Participant told price when appointment was scheduled.
Targeted minority recruitment (advertising and site selection)	• 14 diverse metropolitan sites • Black and Hispanic (with Spanish translations) advertisements

Participants were asked to review a mock-up MEVACOR™ Daily package in a simulated store front situation and make a Self-Assessment (SA) regarding their eligibility per label instructions and a Purchase Decision (PD) regarding their intent to buy the product at that time. Lipid testing prior to making either the SA or PD decision was provided only if the participant requested it. All participants who did not request a test were given one after completing all study questions, to allow for the calculation of Framingham risk scores at a later time. After the SA and PD decisions were made, participants were interviewed about their demography, medical history and rationale for their decisions. Particular focus was placed on those who made a positive SA or PD but were ineligible according to one or more elements of the carton label. Study participants who were incorrect in SA were asked key questions to gain an understanding of why consumers take the actions that they do. Only after all decisions and answers to questions were captured, was the participant informed that the product was not presently available for purchase.

2.3.1.4 Results

Demographics

The advertising campaigns for SELECT and CUSTOM were very effective in recruiting interested individuals. As summarized in Table B-4, 4874 consumers visited one of the two storefront sites in their area. The consumers that responded to the study recruitment advertising are likely to be representative of 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 B-4. In summary, the study advertisements were effective in recruiting an ethnically diverse population.

Table B-4
SELECT and CUSTOM
Demographic Characteristics

	SELECT Study (Protocol 086)	CUSTOM Study (Protocol 084)
Number of participants visiting study sites	1528	3346
Number of evaluators[†]	1499	3316
Males	722	1943
Females	776	1373
Mean age (years)[‡]		
Enrolled/qualified	56.0	56.5
Nonenrolled/nonqualified	~50.6	51.7
Racial origin of Evaluators	N (%)	N (%)
White	940 (62.7)	2373 (71.6)
Black	365 (24.3)	626 (18.9)
Asian	31 (2.1)	68 (2.0)
Hispanic	113 (7.5)	169 (5.1)
Other/unknown	50 (3.3)	80 (2.4)

[†] For this table, evaluators are defined as those who completed the study in SELECT, and those who provided a purchase decision in CUSTOM.

[‡] For this table, enrolled/qualified is defined as "Yes" Purchase Decision in SELECT (N=431) and as Users in CUSTOM (N=1061). Nonenrolled/nonqualified is defined as "No" Purchase Decision in SELECT (N=1065), and as Non-Purchasers in CUSTOM (N=2111).

Overall Results

The SELECT study showed meaningful improvement in self-selection by women < 55 years of age and childbearing potential while performing similarly to CUSTOM regarding low CHD risk consumers. In addition, self-selection for participants with safety ineligibilities remained low and comparable to the strong CUSTOM scores. Table B-5 shows a summary of the above results in the areas targeted for improvement in SELECT when compared to CUSTOM.

Table B-5
Summary of SELECT and CUSTOM Comparisons

Criteria	SELECT (%)	CUSTOM (%)	% Change
Women < 55			
Women <55 who elected to use (PD=Yes, incorrect)	12	23.4	50
Women electing to use who were <55 (PD=Yes, incorrect)	25.5	37	30
Women of Childbearing Potential			
Pregnant or Breastfeeding (PD=No, correct)	100	NA	NA
Women <45 electing to use the product (PD=Yes, incorrect)	5.3	15	70
Low CHD risk Users (PD=Yes) with <5% Framingham risk score	29	27	No Change
Low-risk men	11	11	No Change
Low-risk women	47.8	51	No Change

Women <55 Years

A small percentage of women <55 years who evaluated the product made incorrect self-assessment (11.1%, 42/377) or purchase decisions (12.4%, 48/387). This is a notable improvement (approximately 50%) over CUSTOM. Additionally, of those 42 women who made an incorrect self-assessment decision in SELECT, 50% were within 4 years of age 55. Of the 48 women <55 years of age who made an incorrect purchase decision in SELECT, 44% were within 4 years of age 55. In comparison to CUSTOM where 37% (161/430) of the female user population were women <55 years of age, in SELECT 25.5% (48/188) of the females who made a positive purchase decision were <55 years of age.

Women of Childbearing Potential

With this substantial reduction of the percentage of women <55 years of age who would incorrectly purchase, the product label helps to effectively minimize the number of women of childbearing potential who would be exposed to the drug. The label effectiveness was demonstrated by the fact that 100% (26/26) of the women who were pregnant, breast-feeding, or indicated that they may become pregnant correctly decided not to purchase. Unlike CUSTOM, the SELECT label contained a warning against use if "*you may become pregnant*", and this message was effective in guiding all 21 women who said they might become pregnant to decide correctly not to purchase. Looking at the group of women under 45 years of age (the age where unintended pregnancy is more likely to occur), there was an approximate 70% improvement over CUSTOM (15% of

women less than 45 years elected to use the product versus 5.3% in SELECT). Again, substantial improvement was brought about by changes made to the label.

Low CHD Risk

The third goal of SELECT was to reduce the proportion of low CHD risk (<5% risk of CHD in 10 years) purchasers. For this goal, SELECT did not appear to demonstrate an improvement over CUSTOM. Instead, results were very similar despite the significant decrease in the number of women less than 55 who wanted to purchase. Of the participants with low CHD risk, 73% (382/520) decided that MEVACOR™ Daily was not appropriate for them and 78% (421/536) decided not to purchase the product. However, to be consistent with CUSTOM, it is necessary to look at the number of participants in SELECT who responded PD=Yes, of which 27% (115/419) were of low CHD risk. In CUSTOM, 27% (289/1059) of the product users had CHD risk <5%. As with other areas of interest, there may have been an improvement in SELECT over CUSTOM in the proportion of low-risk evaluators who elected not to purchase. However, in CUSTOM, Framingham Risk Scores were not calculated on consumers who elected not to purchase, so that comparison is not possible.

Of the 536 participants with CHD risk <5% who provided a purchase decision, 409 were female (76.3%) and 127 were male (23.7%). Despite this unbalanced gender distribution, the proportion of these participants who decided not to buy (PD=No) was virtually identical for this CHD risk <5% group: 78.5% (321/409) for females and 78.7% (100/127) for males. For the population who said they wanted to purchase (PD=Yes), 11.4% (27/237) of males had a calculated CHD risk <5%, and 48.4% (88/182) of females had a calculated CHD risk <5%. These results are comparable to CUSTOM, in which 11% of male users and 51% of female users had a calculated CHD risk <5%. The relatively low proportion of low-risk males is identical in both SELECT and CUSTOM. This shows that the label properly excluded low-risk males and that 11% is a reasonable expectation of a lower limit beyond which major improvement may not be achievable. We are committed to providing additional tools in market such as a risk calculator at the MEVACOR™ Daily website to provide additional communication about high and low risk to drive even more informed choices.

The uneven distribution of CHD risk <5% between females and males may be more a function of the Framingham risk calculation rather than deviation from the product label. As noted, the package label for nonprescription lovastatin was developed to be consistent with NCEP ATP III Guidelines for primary prevention using pharmacological treatment in individuals who were male ≥45 years of age or female ≥55 years of age with LDL-C ≥130 mg/dL and at least one additional CHD risk factor. (In the SELECT Total-C paradigm, Total-C ≥200 mg/dL was a surrogate for LDL-C ≥130 mg/dL, and women were still required to have one additional risk factor.) Thus, an individual, especially a female, could meet the label criteria for treatment with nonprescription lovastatin, and yet have <5% 10-year CHD risk according to the Framingham CHD Risk Score calculation. Additionally, family history, which is a widely accepted CHD risk factor, is not part of the Framingham Risk Score calculation. One approach to correct this could be to change the label to increase the age of eligible females from 55 to 65 years of age, thus reducing

the proportion of low-risk women (as defined by Framingham risk scores). However, this is counter to NCEP ATP III Guidelines, and recent AHA Guidelines which recommend far more aggressive treatment of women, and thus this label change is not recommended. In fact, the lower-risk female population seen in SELECT is actually consistent with the more recent AHA Guidelines for Women, (see below) suggesting that the SELECT results may be viewed far more favorably in this context.

Worldwide, CHD is the largest single cause of death among women, accounting for one third of all deaths. In many countries, including the United States, more women than men die every year of CHD. Some factors that may contribute to female risk of CHD that are not included in the Framingham Risk Assessment or in the NCEP ATP III Guidelines include poor diet, physical inactivity, obesity, evidence of subclinical vascular disease, metabolic syndrome, and poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise [23]. Studies have demonstrated that a low Framingham Risk Score guarantees neither the absence of atherosclerotic cardiac disease (as measured by coronary artery calcification) nor the absence of a cardiac event in the short- or long-term future and that the Framingham Risk Score particularly underestimates disease risk in women [24; 25; 26; 27]. In an effort to improve risk estimation and subsequently the treatment of women, an expert panel had developed the Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women. This AHA update acknowledges that women with one or more risk factors may have a broad range of cardiovascular disease risk [23]. The update advocates placing greater emphasis on lifetime risk as opposed to the short-term absolute risk defined by Framingham Risk Score and suggests that even woman 50 years of age with a single risk factor have a significant increase of lifetime cardiovascular disease and death. Additionally, a publication of a re-analysis of AFCAPS/TexCAPS data in light of the NCEP ATP III Guidelines showed that treatment of lower-risk patients (mean 10-year CHD risk of 6.4% as determined by the event rate in the placebo group, not Framingham) with lovastatin decreased the relative risk of a cardiac event by 34% [4]. Careful evaluation of risk factors, including obesity and physical inactivity, may better identify those who would benefit from lipid lowering therapy than Framingham Risk Scores. While these data were not collected in SELECT, this information supports the conclusion that the CHD risk of the females in the SELECT study (and in the female population in general) is underestimated by the Framingham Risk Assessment.

Safety and Benefit Criteria

The SELECT study also maintained the high scores based on the safety elements of the label that were achieved in CUSTOM, and demonstrated that 100% (based on PD) of the participants adhered to the label's absolute safety criteria (pregnancy, breastfeeding, childbearing potential, and allergy to lovastatin).

The majority of participant label ineligibilities were related to benefit criteria. For both LDL-C and Total-C paradigm participants with incorrect self-assessment, approximately 83% made benefit errors only. For both paradigms, of participants with an incorrect purchase decision, approximately 91% made benefit criteria errors only. Since not all criteria may be equally important, the label elements were prioritized into different

hierarchies. The safety hierarchy groupings were based on absolute contraindications and relative contraindications that are stated on the label, and the safety criteria were prioritized as follows: pregnant/breast-feeding, may become pregnant, allergy to lovastatin, interacting medications, lipid-lowering medications, and liver problems. Table B-6 summarizes participants with a positive purchase decision (PD=Yes) who met the specific label safety criteria identified sequentially on each line. If a participant did not meet the specified criterion, they were excluded from the counts on the line and were not assessed for the next identified label criterion. As shown in Table B-6, the purchase decision results are extremely strong (over 90%) when all safety components are factored into a hierarchy.

Table B-6

Purchase Decision vs. Eligibility Based on Safety Hierarchy

LDL-C and Total-C Paradigms

	LDL-C Paradigm		**Total-C Paradigm**	
	PD=Yes (N=196)[†] **Correct vs. Specific Label Criteria**		**PD=Yes (N=223)[†]** **Correct vs. Specific Label Criteria**	
Label Criteria	**n**	**%**	**n**	**%**
Not Pregnant/Breast-Feeding	196	100	223	100
May Not Become Pregnant	196	100	223	100
Not allergic to Lovastatin	196	100	223	100
No Interacting Medications	195	99.5	221	99.1
No Lipid-Lowering Medications	183	93.4	208	93.3
No Liver Problem	181	92.3	207	92.8

[†] Participants with missing data, participants whose eligibility could not be determined due to a data collection issue, and protocol violators are excluded.

Reasons for Participant Decisions

One of the objectives of the SELECT study was to understand the participant thought processes when making their self-assessment and purchase decisions. From the many years of testing MEVACOR™ for over-the-counter use, we have learned that some people will knowingly make "incorrect" decisions and it was a key objective of SELECT to understand why. To achieve this objective, many open-ended questions were asked when participants made decisions that would appear to be incorrect. These open-ended responses have captured many of their reasons behind their decisions and show that there is a thought process that makes sense to them. Participants are in fact interpreting the label with regard to their own personal histories, and in ways that did not compromise

safety. In order to put participants' decisions into perspective, the label criteria were divided into three categories:

- Benefit – age too young, lipid values out of range or unknown, history of stroke or heart disease, current diabetes, planning to substitute MEVACOR™ Daily for current Rx cholesterol medicine, no additional CHD risk factors
- Relative Safety Contraindications – taking potentially interacting drugs, current liver disease, planning to take MEVACOR™ Daily concomitantly with current Rx cholesterol medicine, drinking large quantities of grapefruit juice
- Absolute Safety Contraindications – allergic to lovastatin, pregnant or breastfeeding, may become pregnant

In SELECT most of these decisions, in which the participant decided to "override" the label, were made as deviations from benefit criteria, while only a few participants did so related to safety criteria. This resulted in 100% correct decisions for absolute contraindications and over 90% correct for relative contraindications for purchase decision. The most common "override" for benefit was lipid values. The advertising for the SELECT study targeted consumers who were concerned about cholesterol. Many of these consumers have learned that they have high cholesterol and may be more apt to override the lipid values on the label and to try MEVACOR™ Daily. Furthermore, some participants said they would talk with their doctor about their ineligibility either before buying or before using the product. Participants felt they were still following the label when choosing to do this since the label clearly states, "Ask a doctor or pharmacist before using if…" for all label elements except for the absolute safety elements. Other reasons that offer insight include "told by doctor I should be treated," "I am close to (age, LDL-C, Total-C, HDL-C)," "I will get/check my cholesterol numbers before using," and "I have a family history of heart disease."

Other participants demonstrated clearly that they misunderstood the self-assessment question. A typical example of this occurred when a participant stated that they were appropriate for the product but that they did not want to buy the product. When asked why they decided not to buy the product, many responded that they did not meet an eligibility criterion, thus demonstrating that they knew the product was not appropriate for them.

Differences in SELECT and CUSTOM Study Designs

The previously noted strong improvements in self-selection results compared to CUSTOM were achieved despite additional challenges created by the SELECT study design. In SELECT, in order to test participants' ability to self-select with the minimal amount of information that would always be available at the purchase site, only the product carton label was available. In CUSTOM, participants had the ability to use the proposed in-market decision-making tools including tear pads, decision wheels and had access to a 1-800 number and a website for advice. In addition, participants in CUSTOM were given help with eligibility assessments by the investigators playing the role of a pharmacist if the consumer requested it. Participants in CUSTOM were also able to leave the site and speak to their doctor for advice and had additional opportunities to

obtain lipid values. Finally, in CUSTOM, participants had access to the educational materials in the box (post purchase). None of these features were available to the participants in SELECT. Consumers in the marketplace would have access to all of these additional program components both pre and post-purchase. In fact, 90% of participants in CUSTOM used one or more of the above aides that were available to them. Thus, the results of SELECT could be considered a "worst case scenario." Despite these purposeful restrictions to providing real-world access to product information and consumer-friendly guidance, the SELECT study showed notable improvement in two of the three areas where improvement was the goal. Using this conservative approach, SELECT showed that participants could make appropriate decisions with the box alone, even without physician input.

Overall Evaluation of Self-Selection

Besides the comparisons to CUSTOM, the SELECT study was designed to evaluate the overall self-assessment and purchase decisions of consumers. For participants to be classified as correct for overall self-assessment and purchase decisions, they had to meet every one of the 15 label eligibility criteria that applied to them. The 15 label eligibility criteria are listed in Table B-7.

Table B-7

MEVACOR™ Daily Label Eligibility Criteria

Label Eligibility Criteria	Comment
Age in range	
Not pregnant or breast-feeding	Applies to women only
May not become pregnant	Applies to women only
No heart problem/disease	
No stroke	
No diabetes	
No liver disease/liver problem	
Not allergic to lovastatin	
Not taking lipid-lowering medication	
Not taking listed potentially interacting medications	
LDL-C/Total-C value in range	
HDL-C value in range	Applies to women only
Do not drink large quantities of grapefruit juice	
Used cholesterol numbers from fasted test	
Have at least one additional listed CHD risk factor	Applies to women in LDL-C and Total-C paradigm, and to men in LDL-C paradigm only

The majority of participants made correct self-assessment and purchase decisions (72% and 77%, respectively). The revised label was very effective in turning away ineligible consumers. Ninety-eight percent of those who said SA=No had an ineligibility, and 96% of those who said PD=No had an ineligibility. The majority of those who said PD=No cited not meeting eligibility criteria, and 15% wanted to talk to a doctor, which for most ineligibilities is according to label. However, 78% of those who said SA=Yes and 80% of those who said PD=Yes were considered incorrect because their decision was not 100% correct on all 15 label elements with their eligibility assessment. This strict analysis does not take into account any open-ended responses provided by the participant, such as intent to talk to their doctor before use, or recognition that they were close to meeting a seemingly arbitrary numerical cut point (e.g., age or lipid value). Additionally, it is extremely important to note that only about 9% of the incorrect purchase decisions were potential safety errors. When potentially mitigating factors are considered (such as intent to talk to doctor as directed by the label), the percentages of correct decisions are even higher. It is encouraging to find, however, that in the LDL-C paradigm approximately 76% were correct for SA and PD on 13 of 15 label elements, and in the Total-C paradigm 79% were correct for SA and PD on 13 of 15 label elements (again noting that the vast majority of the errors were made on benefit and not safety criteria).

Comparison of LDL-C and Total-C Label Paradigms

Two label paradigms were tested in SELECT. One was based on LDL-C and the other was based on Total-C, a possibly more consumer-friendly surrogate for LDL-C. The purpose was to determine if, given the familiarity of Total-C with consumers, the Total-C label paradigm would generate better consumer decision making behavior.

There were meaningful differences in the correctness of SA=Yes decisions regarding LDL-C and Total-C lipid criteria, and in the total correctness of SA=Yes and PD=Yes decisions. For participants who said SA=Yes, in the LDL-C paradigm 36% of participants were in the correct LDL-C range, compared to the Total-C paradigm where 50% were in the correct Total-C range. In addition, 28% of participants who said SA=Yes in the LDL-C paradigm did not know their LDL-C values, compared to only 11% of SA=Yes participants in the Total-C paradigm who did not know their Total-C values. When overall SA=Yes and PD=Yes values were compared, the Total-C label appeared to have performed better. For SA = Yes, 16% were completely correct in LDL-C vs. 27% completely correct in Total-C. For PD=Yes, 15% were completely correct in LDL-C vs. 25% for Total-C.

These observed differences favoring the Total-C label may be due to consumers being more familiar with their Total-C values than LDL-C and the Total-C label being more "consumer friendly." However, when the overall proportions of corrects are compared, there is a smaller difference between the labels (about 71% for SA and 77% for PD for both label paradigms). Additionally, when the data are examined in different ways such as with hierarchies and mitigating factors, the differences between the two labels are less evident.

Cholesterol Knowledge

Among consumers who did not know their lipid values in the LDL-C paradigm, about 22% said that MEVACOR™ Daily was right for them (SA=Yes) and 19% would purchase (PD=Yes). Numbers in the Total-C paradigm were slightly better (about 18% for SA and 14% for PD), perhaps reflecting improved consumer knowledge of Total-C over LDL-C (and possibly due to the large amount of direct to consumer advertising for lipid lowering medications on television which targets Total-C and not LDL-C). Despite this, approximately a third of these consumers fell into the appropriate LDL-C or Total-C ranges that would make them eligible to use MEVACOR™ Daily.

All participants who came to the site knew this was a clinical study and there may have been an expectation that they would be given a cholesterol test prior to any drug being dispensed. When they contacted the call center for an appointment, everyone was told to come to the storefront site fasted with the explanation that diagnostic safety tests would be done. This may have been interpreted by the participants that they would be given a cholesterol test automatically when, in fact, they would need to request one. This may explain why some participants made decisions without knowing their numbers or why some participants asked for a test between making their SA and PD decisions (when they realized that they would not automatically receive a cholesterol test, they inquired about getting one).

It is important to note that in the United Kingdom where ZOCOR Heart Pro™ is available without a prescription, consumers do not need to know their cholesterol numbers and eligibility is determined by self-identification of risk factors and age. This paradigm was driven by the results of the simvastatin Heart Protection Study (HPS) which was a mega-trial demonstrating, among other things, that CHD risk was reduced similarly across the treatment group regardless of baseline lipid values. In fact, a statement to this effect is in the FDA approved US labeling for ZOCOR™.

Because of the importance of consumers knowing their cholesterol number, Merck is committed to providing consumers with information on how they can get an initial test and obtain pre-treatment cholesterol test results. The Cholesterol Testing Referral Service will direct consumers to the nearest testing locations (clinic, pharmacy, or laboratory) via zip code and will be available to consumers through the pre-purchase consumer assistance program. This referral service will also encourage follow-up testing. (Please see Section C. for further details.)

Overall Effectiveness of the Label and Average User

The average participant who responded SA=Yes was 7.5 years older than the minimum age for use indicated on the label (the average male was 10 years older and the average female was 5 years older), had LDL-C within the range indicated on the label, and had an average of approximately 2 CHD risk factors. The data for the LDL-C and Total-C paradigms individually are very similar. Thus, the label was very effective in communicating the requirements for use of the product to the consumer and drove consumers into the desired range for lipids and age.

The typical participant who responded SA=Yes had a primary care physician, health insurance, tried diet and exercise, was well educated, and was middle class based on annual income.

Overall, there appeared to be little effect on behavior based on race, gender, and literacy (based on REALM testing). Although there were some differences observed with age (more older participants made incorrect decisions), it is difficult to conclude that this is meaningful due to the small numbers of participants with positive SA or PD in each age group.

Heart Disease, Stroke, and Diabetes

On average, about 30% of participants with a history of heart disease, stroke, or diabetes wanted to purchase the product (the proportions are similar for SA and PD as well as LDL-C and Total-C label paradigms and similar to the results in CUSTOM) and approximately two-thirds (SA=Yes) to three-quarters (PD=Yes) of these participants were not taking any lipid lowering medication. These participants are considered at higher CHD risk and should be treated with a statin. While MEVACOR™ Daily might not be the correct dose for these participants, some type of treatment is warranted, and the 20-25% reduction in LDL-C would still provide substantial, albeit not optimal, benefit. Nearly two-thirds of these participants were not currently taking any prescription lipid-lowering medication. Furthermore, the Self-Management System program was shown in CUSTOM to drive 74% of these high risk people to see their doctor about lipid management.

Opportunity for Improvement

One area of concern seen in SELECT was the prevalence of evaluators already taking a lipid lowering medication. About 33% of these evaluators said that MEVACOR™ Daily was right for them (SA=Yes) and about 22% would purchase it (PD=Yes). There is a large drop-off in the proportion of consumers when going from SA=Yes to PD=Yes in this case (from 33% to 22%). Based on open-ended responses, it appears that there may have been a misunderstanding of the SA question. Many consumers said that MEVACOR™ Daily was right for them thinking that, since they were already on a lipid lowering medication, they were already appropriate to use any lipid lowering medication. When it came time to purchase, many said that they did not want to purchase since they were already using such a medication. Although the numbers are small for PD (consumers saying they want to buy it), 8 of 27 (LDL-C) and 8 of 31 (Total-C) consumers said they would take MEVACOR™ Daily along with their present prescription lipid lowering medication and 14 of 27 (LDL-C) and 18 of 31 (Total-C) said they would take MEVACOR™ Daily in place of their prescription lipid lowering medication. These results may be due to insufficient emphasis in the label. Although the label directs consumers who are on a lipid lowering medication to ask a doctor before use and not to substitute, there is no warning not to take concurrently. Interestingly, in CUSTOM 30% (213/714) of evaluators who were on a lipid lowering medications elected to use the product. Thus, there was an improvement in SELECT (22% PD=Yes) over CUSTOM. This may be due to the added language in the warning section of the

label that states "This product is probably not strong enough for you" which was not in the CUSTOM label. Nonetheless, stronger language should be included on the label and support materials to further warn consumers not to substitute or take along with prescription lipid lowering medication and inform them of the consequences of doing so. Merck will work with FDA to develop and test stronger label language and further reinforce this message in all elements of the support system. With regard to substituting MEVACOR™ Daily for prescription lipid-lowering medication, Brass et al. demonstrated in a publication based on CUSTOM data that even when taking into account those who are diverted from optimal care to OTC, the public health benefit of the availability of MEVACOR™ over-the-counter is still evident. [28].

Study Design Limitations

While the SELECT study was designed to be naturalistic as possible, it is often difficult to achieve this. Participants know that they are participating in a supervised clinical study and thus might believe that they will be protected from their mistakes ("They won't let me do anything dangerous"). Additionally, based on some of the open-ended responses of participants who were either already on a statin, had been given a prescription for a statin that was not yet filled, or who recently lost their prescription benefit insurance, many participants were looking for a way to obtain a lipid lowering drug at a reduced cost.

Some aspects of SELECT contributed to limitations in interpreting the data. Even though SELECT relied upon computer data entry and a complex computer algorithm to minimize data (and human) error, some procedural errors still occurred. There were a relatively small number of participants who were supposed to have been asked follow-up questions regarding incorrect decisions, but were not asked these questions. This occurred largely due to investigator errors. Unfortunately, this prevented further understanding of these participants' incorrect decisions. A study design element regarding eligibility assessment was that the label stated, "Ask a doctor before use if you…have diabetes." However, the eligibility assessment question asked if the participant currently had diabetes or high blood sugar. Therefore, some participants responded yes to this question when they did not actually have diabetes. Some of these were rectified based on open-ended responses, but the diabetes ineligibility may have yielded artificially high rates of apparently inappropriate self-selection.

2.4 Consumer Behavior During Treatment

2.4.1 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.

2.4.1.1 Behavior Regarding Follow-Up Cholesterol Test

In CUSTOM, 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 nonprescription lovastatin.

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) were at 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.

2.4.1.2 Management of Potential Safety Risks

2.4.1.2.1 Behavior During Actual Use

There were 366 Users in CUSTOM that began a new prescription, experienced a new medical condition or developed unexplained muscle pain. Of these, 345 (94%) adhered or closely adhered to the label directions regarding the continued use of nonprescription lovastatin and informing a physician. Further information on the 21 Users that did not adhere to the label criteria is provided below. In most cases the explanatory information indicated no potential for safety concern.

New Prescription

Two Users were given new prescriptions for a presumed infection (clarithromycin) without informing their physician about nonprescription lovastatin; however, both correctly stopped taking nonprescription lovastatin when they began taking the antibiotic. Thus, neither User had the potential for safety concern.

New Medical Condition

Three Users developed CHD, diabetes, or stroke and did not inform their physician about nonprescription lovastatin; however, 2 of the 3 had a valid reason for not doing so. Thus, only one User's behavior had the potential for safety concern.

Unexplained Muscle Pain

Of the 63 Users who developed unexplained muscle pain in CUSTOM, 47 (75%) acted appropriately. The remaining 16 Users developed unexplained muscle pain and neither discontinued nonprescription lovastatin nor informed their physician about nonprescription lovastatin; however, 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").

2.4.1.2.2 End of Study Scenario Testing

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.

Opportunity for Improvement

The data from the actual use of nonprescription lovastatin and the end-of-study scenario testing in CUSTOM indicated that, although the appropriate behavior regarding development of unexplained muscle was good (81%, 75%, respectively), there was potential for improvement. In addition, as mentioned earlier in section 1.2, FDA requested labeling changes to improve compliance with the muscle warning during ongoing use. Therefore, the internal package materials were modified and "refrigerator magnet" was developed to contain a more thorough explanation of the condition and possible consequences of not heeding the warning. These modifications were tested in Muscle Warning Comprehension Study #088, the results of which were summarized in section 1.2.

2.4.2 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. In the OTC environment the ultimate goal of encouraging consumer interactions with health care professionals is to establish a partnership in the management of cholesterol. Although physician interactions are encouraged by the MEVACOR™ Daily Self-Management System, it is realistic to recognize that self-motivated consumers might attempt to manage cholesterol on their own. Data on consumer interactions with physicians was collected in the CUSTOM actual use study and in the lovastatin 10 mg actual use studies, and these data are summarized below.

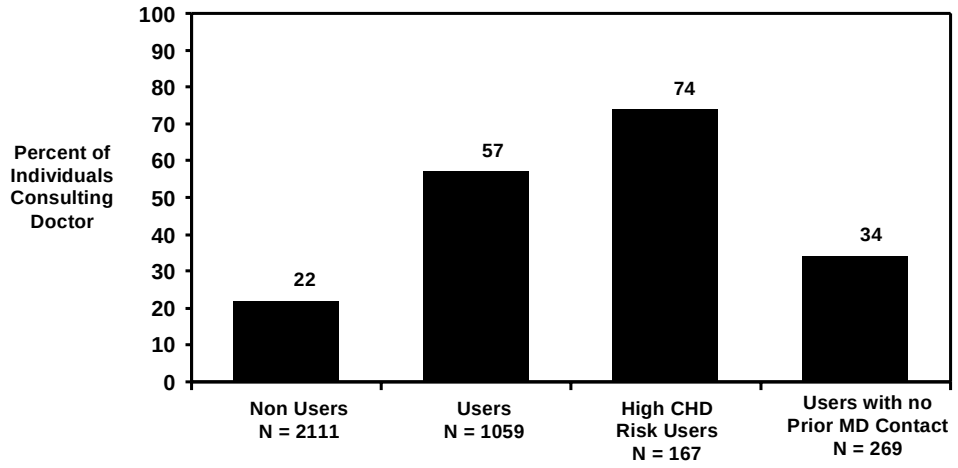
CUSTOM Study #084

Figure B-1 visually depicts some of the key results regarding participant interactions with physicians. Physician interactions were reported by 42% of Purchasers before beginning therapy with nonprescription lovastatin 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 nonprescription lovastatin. 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 nonprescription lovastatin to lower cholesterol despite the restrictive labeling and relatively complex self-management rules.

The nonprescription lovastatin 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 Self-Management System successfully directed many cholesterol-concerned individuals into the health care system who may not have had such physician contact otherwise.

Also, although clearly recognized in the nonprescription lovastatin product label as being inappropriate for OTC therapy without first consulting with a physician, 70 high risk Users (i.e. those with a history of CHD, stroke, or diabetes) decided to take the product. 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 nonprescription lovastatin. Thus, 74% (123 of 167) of high risk Users interacted with a physician during CUSTOM.

Figure B-1
CUSTOM: Physician Interactions



Results from CUSTOM provide evidence that the nonprescription lovastatin Self-Management System helped to direct Evaluators considered by the label to be ineligible for nonprescription lovastatin with either LDL-C >170 mg/dL or triglycerides >200 mg/dL to seek professional care. As part of the Self-Management System, 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 Self-Management System 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 nonprescription lovastatin, 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 an appointment with a doctor which had not yet occurred at the time of the survey. 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 understood with 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).

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.

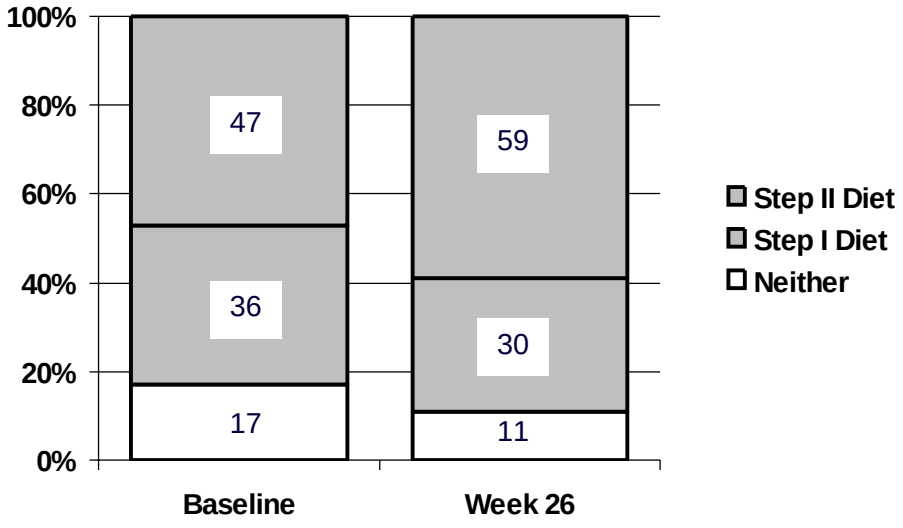
2.4.3 Heart-Healthy Lifestyle Behaviors

Heart-healthy behavior was evaluated in the CUSTOM #084 and Pharmacy #076 actual use studies. The results show unambiguously that access to an OTC statin did not result in deterrence from appropriate diet and exercise behavior.

CUSTOM Study #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 nonprescription lovastatin, 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 B-2).

Figure B-2
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 Self-Management System 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 nonprescription lovastatin 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 nonprescription lovastatin 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 nonprescription lovastatin 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 will be expanded to allow access to all interested consumers, not just those that exactly fit the restrictive label criteria.

Pharmacy Study #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.

2.4.4 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.

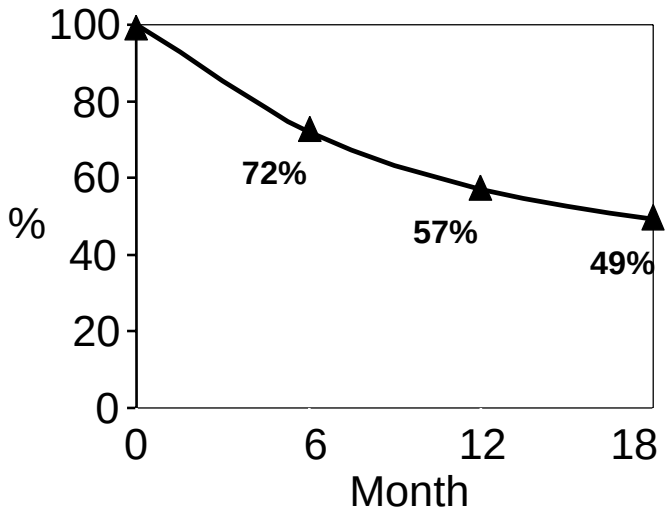
Two of the nonprescription lovastatin use trials summarized in this application were of sufficient design and duration to gain some insight into consumers' persistence and compliance behavior in an OTC environment. The Pharmacy Study (Protocol 076) evaluated the use of lovastatin 10 mg over a 6-month 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 surrogate measure to estimate overall compliance with regular dosing. The results from these studies are summarized below.

2.4.4.1 Pharmacy Study #076 and Extensions

Persistence

Persistence with study drug therapy was assessed in all 722 participants who were initially dispensed study drug (lovastatin 10 mg). One way to define persistence is to evaluate 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 B-3 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 B-3
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 supported by 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.

2.4.4.2 CUSTOM Study #084

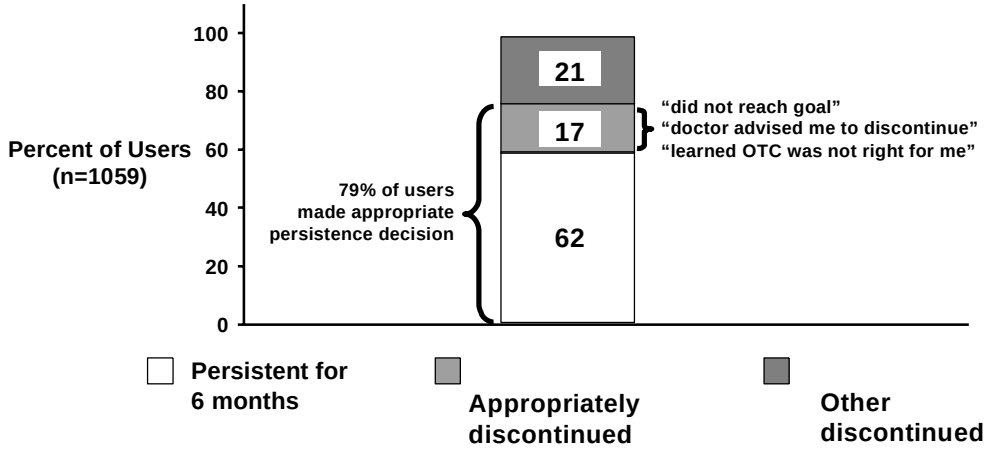
Persistence

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 remained in the study for 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 B-4, 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 B-4
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 direct 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.

2.4.4.3 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 the study sites, making study drug re-supply more difficult (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). These discontinuations, although label-appropriate, would adversely impact persistence as defined.
- 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 [29; 12; 30; 31]. Specifically, Jackevicius et al. [31], 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 [12; 30]. 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 [32]. 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 50% [33] to 64% [34] of participants who persisted on therapy at 1 year in those studies was very consistent with the 57% persistence rate observed in the Pharmacy Study simulated OTC environment.

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.

2.4.4.4 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.

- Long-term persistence and compliance with lovastatin in a nonprescription setting compares favorably with published literature on experience with prescription statins.
- There is little 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.

2.5 Discussion

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 SELECT Study, 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, and Merck is committed to implementing a comprehensive Self Management System comprised of 10 key components which provide multiple pathways for reaching consumers. Most of these components have been tested and demonstrated to be successful in the CUSTOM study. (See Section C. MEVACOR™ Daily Self-Management System and Marketing Plans for details of the Self Management System's 10 components.)

SELECT demonstrated that the majority of participants evaluating MEVACOR™ Daily made correct self-assessment and purchase decisions (72%, 77%, respectively). When potentially mitigating factors are considered (such as intent to talk to doctor as directed by the label), the percentages are even higher. Notable improvements over CUSTOM were observed in the percentage of women <55 years who evaluated the product and made incorrect purchase decision, and in the percentage of women <45 years who elected to use the product.

The majority of Users in CUSTOM (i.e. those that purchased and took at least 1 dose of MEVACOR™ OTC) demonstrated acceptable ongoing use behavior regarding treatment-to-goal, compliance/persistence, and changes in health status. Long-term persistence levels comparable to prescription use were demonstrated in both CUSTOM and the 18-month Pharmacy Study (Protocol 076).

Throughout the 26 week duration of CUSTOM, only 2% of Users demonstrated behavior that created the potential for suboptimal safety, and no serious drug-related adverse events resulted, consistent with the large safety margin associated with the 20 mg dose of lovastatin. After 26 weeks, median LDL-C was reduced by 25% among those that fasted prior to testing, with 62% of those tested achieving LDL-C target goal (<130 mg/dL).

Physician-study participant interactions were common in CUSTOM: 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 nonprescription lovastatin, and 22% reported a physician interaction regarding nonprescription lovastatin 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. The results regarding physician interactions from CUSTOM are supported by findings from the nonprescription lovastatin 10-mg use studies (Protocols 076 and 081). Nonetheless, CUSTOM and SELECT make clear that physician involvement is not a requisite for safe and effective self-management of moderately elevated cholesterol.

At study end of CUSTOM, 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. These results are consistent with self-reports from the Market Research Add-on Questions in the Pharmacy Study, where 91% of participants said they maintained or improved dietary patterns (51%, 40%, respectively) and 94% said they maintained or improved exercise habits (76%, 18%, respectively). Thus, participants showed no evidence of using the medication as an excuse to lessen their adherence to a healthy lifestyle.

The data from CUSTOM demonstrate that the MEVACOR™ Daily 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™ Daily Self-Management System by guiding the overall decision making and self-referral to professional assistance when appropriate. By and large, the targeted population of intermediate risk consumers is able to choose to use MEVACOR™ Daily and achieve LDL-C lowering and treatment-to-goal at rates similar to established medical care benchmarks. Moreover, the overall potential for safety concerns is minimal for consumers using the MEVACOR™ Daily Self-Management System coupled with the strong safety profile of the 20 mg dose of lovastatin.

Points to Consider

Given the multi-factorial approach proposed for consumer behavior optimization with nonprescription lovastatin, it should come as no surprise that a substantial number of participants who wanted to purchase in SELECT did not meet all of the specific label eligibility criteria relating to benefit. For this reason, some may interpret the outcome of the SELECT study as relatively negative if assessed only in terms of pure label compliance. However, 100% adherence to each aspect of the selection criteria is not critical to appropriate self-selection for the 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 of only a few messages or criteria are often independently important. Indeed, in both SELECT and CUSTOM there was a high level of adherence to the label safety criteria.

Similarly, many of the participants with a positive purchase decision in SELECT and 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™ Daily. However, analysis of this population suggests a substantial health benefit would be achieved despite the somewhat lower or higher average absolute risk [28]. Thus, the label meets its objectives. While not meeting a high absolute, complete "heeding standard" in the traditional sense, it represents an appropriate and validated OTC label through use of surrogates to reach the intended target population.

2.6 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, but are not required for self-management. 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.

Self-Selection Conclusions from SELECT

1. The SELECT study demonstrated meaningful improvement over CUSTOM regarding self-selection by women < 55 years of age.
2. The SELECT study demonstrated that pregnant or breastfeeding women and women of childbearing potential would elect not to purchase the product.
3. Although 29% of the participants in SELECT who elected to purchase MEVACOR™ Daily were of lower CHD risk, the majority of these participants were women in whom Framingham Risk Scores may underestimate CHD risk despite being eligible according to the label.
4. The SELECT study maintained the high safety decision scores found in CUSTOM. The majority of label eligibility errors made by SELECT participants were related to optimal benefit and not safety related.
5. The SELECT study achieved strong results for consumers who said the product was not right for them and for those who chose not to purchase. Over 95% of participants who said No to SA or PD were correctly ineligible.
6. Meaningful differences between the LDL-C and Total-C paradigms were seen with overall SA and PD, and with the percent correct SA for lipid criteria (36% correct for the LDL-C criterion versus 50% correct for the Total-C criterion).
7. Stronger labeling language regarding consumers already taking a lipid lowering prescription medication is warranted and will be developed.

Overall Consumer Behavior Conclusions

1. Consumers interested in a nonprescription cholesterol-lowering product are aware of cholesterol as a health risk factor.
2. 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.
3. Consumers' knowledge of LDL-C and Total-C is sufficiently accurate to support appropriate purchase and use decisions.
4. The product labeling and reinforcement tools inherent in the MEVACOR™ Daily 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.
5. Consumers selecting to self-medicate with the product comply well with regular dosing, and a substantial subset will persist on long-term treatment.

6. Therapeutic lifestyle patterns (such as diet and exercise) are encouraged and as a result are maintained or improved with the MEVACOR™ Daily Self-Management System.
7. The MEVACOR™ Daily Self-Management System encourages healthcare professional interactions when appropriate for both users and non-users of the product.

3. SELECT Study Manuscript Submitted for Publication

The following pre-publication draft manuscript on the results of the SELECT Study has been co-authored by Dr. Eric Brass and Dr. Saul Shiffman with members of the Merck team. It is currently under review with the American Journal of Cardiology where it has been submitted for publication.

MANUSCRIPT

Can consumers self-select for appropriate use of an over-the-counter statin? The Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT) study

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ABSTRACT

Background: Access to over-the-counter (OTC) statins has the potential to improve public health by reducing cardiovascular morbidity and mortality. However, data are required to demonstrate that consumers can appropriately decide whether to use these drugs based on their individual health histories and then manage the course of treatment. The Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT) was designed to assess consumers' ability to appropriately self-select for treatment with lovastatin in an unsupervised setting.

Methods: SELECT recruited participants who were concerned about their cholesterol. Participants were allowed to examine proposed OTC lovastatin cartons whose labels detailed an algorithm for self-selection based on age, lipid profile and cardiovascular risk factors. Participants viewed either a carton with an LDL-based self-selection algorithm, or one based on total cholesterol. The labels also contained warnings against use based on health conditions that might increase the risk of adverse events. Self-selection was evaluated from responses to two questions. Participants were asked if the drug was appropriate for their use (self-assessment) and whether they would like to purchase the drug (purchase decision).

Results: A total of 1326 consumers provided self-assessment decisions. After viewing the LDL-based label, 82%, 36% and 82% of those who self-assessed that the drug was appropriate for their use were correct with respect to the age, lipid and risk factor criteria, respectively. Corresponding numbers for the total cholesterol algorithm were 85%, 50% and 75%. An additional 11 % and 17 % were within 20 mg/dL of the label specified LDL and total cholesterol ranges respectively. Approximately 85% of the women less than 55 years old who evaluated the drug indicated the drug was not right for them, and women in this age group made up only 9% of the total group of participants who felt the drug was appropriate for their use. This was a marked improvement compared with earlier trials. The label was also effective in discouraging use by women who were pregnant or who may become pregnant, consumers with liver disease, and those with potential drug interactions.

Conclusions: SELECT demonstrates that consumers can use an OTC drug label in an unsupervised setting to appropriately self-select for self-management of their cholesterol with lovastatin.

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Despite the established efficacy of 3-hydroxymethylglutyryl-CoA reductase inhibitors (statins) in the primary and secondary prevention of cardiovascular morbidity and mortality [1,2], large numbers of patients appropriate for statin therapy based on consensus guidelines are not receiving the drugs [3-5]. It has been suggested that over-the-counter (OTC) access to statins for primary prevention may be an effective strategy for improving treatment rates by improving consumer access, bypassing barriers to care and enhancing public awareness [6-8]. In contrast, it has been suggested that self-management of hypercholesterolemia may be too complex due to the multiple assessments and decisions required to ensure that the patient requires drug treatment, has no contraindications to use, and can modify the drug treatment based on the response to therapy [9-11]. Clinical research designed to assess consumer behavior in a simulated OTC environment can provide data that informs the benefit-risk assessment for a prescription to OTC switch [12] like the one proposed for statins.

Consumer behavior with respect to the key decision points for use of OTC statins has been previously studied in the Consumer Use Study of OTC Mevacor (CUSTOM) [13]. CUSTOM assessed the behavior of over 3,000 consumers introduced to a simulated pharmacy environment in which lovastatin was available for OTC purchase. CUSTOM tested an OTC label with a self-selection algorithm designed to target a population consistent with the National Cholesterol Education Program guidelines for primary prevention and provided data supporting the hypothesis that consumers could self-select for OTC statin therapy based on their own cholesterol concentrations, monitor their cholesterol during treatment, and self-triage based on their response to treatment [13,14]. CUSTOM also yielded information demonstrating that consumers avoided self-management with OTC lovastatin when their personal health status was not consistent with primary prevention with a statin or if they had contraindications to statin therapy [13]. CUSTOM also allowed consumers to purchase and use lovastatin on their own for six months. Importantly, CUSTOM suggested that consumers who used OTC lovastatin maintained or increased appropriate dietary and exercise habits when taking the drug and maintained or increased their interactions with health care professionals concerning cholesterol management. The data from CUSTOM also permitted estimation of the public health impact of OTC statin access in reducing cardiovascular morbidity [15].

Many of the specific results from CUSTOM were consistent with OTC lovastatin being safe and effective when used in an OTC setting without professional supervision [13,14]. However, the CUSTOM results also demonstrated relative weaknesses in the OTC label used in that study. Specifically, 15% of the participants in CUSTOM who purchased and used the drug were women under the age of 55 despite a label self-selection criterion that users be over age 55 [16]. This cohort was not included in the targeted OTC primary prevention population due to their typically low absolute cardiovascular risk. Driven in part by the use of the drug by younger women, the consumers who self-selected to purchase and use OTC lovastatin in CUSTOM included 27% whose Framingham 10-year estimated cardiovascular risk were under 5% [15]. Additionally, use by women under the age of 55 might expose women of child-bearing potential to lovastatin whose safety during pregnancy has not been established.

Based on the results from CUSTOM the proposed OTC label for lovastatin was modified. These modifications included clear statements on the front panel that the drug was for women age 55 and older or men 45 and older and an improved warning against use during pregnancy printed on the back label. Other changes were made to clarify the algorithm for self-selection based on cholesterol concentrations and cardiovascular risk factors. To better understand the bases for consumer decision making, labels utilizing either LDL or total cholesterol criteria were developed for comparison purposes. The effectiveness of these label changes in facilitating consumer self-selection for self-management with OTC lovastatin were studied in the Self Evaluation of Lovastatin to Enhance Cholesterol Treatment (SELECT) study.

METHODS

Overview

SELECT was a self-selection study designed to simulate consumer behavior in a real-world OTC setting. Consumers were recruited and provided an opportunity to examine the OTC lovastatin carton before making a self-selection decision. The self-selection process was broken down into two related components. The first component was self-assessment, and recorded the response to "Based on this label, is this product appropriate for you to use right now or not?" The second component was the purchase decision and was recorded as the response to "Would you like to pay for this right now for your own use or put it back in the display?" To minimize bias, data collection and investigator-participant interactions were limited until after the self-assessment and purchase decisions. Based on the self-assessment and purchase decisions the study's prospectively defined primary objectives were to assess the ability of the new label to minimize self-selection by three consumer groups: 1) women under the age of 55; 2) women who are or who may become pregnant; and 3) consumers with low absolute cardiovascular risk defined as a 10-year Framingham Risk Score of less than 5%. A secondary objective was to assess the effectiveness of LDL and total cholesterol algorithms in consumer decision making.

Label self-selection criteria

The proposed OTC labels used in SELECT were designed to support consumer self-selection for safe and effective use of lovastatin for primary prevention of cardiovascular morbidity and mortality. Each label contained instructions for self-selection intended to simulate the National Cholesterol Education Program (NCEP) treatment recommendations [17]. Thus, the label guided the consumer through decision branch points based on their gender, age, LDL or total cholesterol concentrations and the presence of additional risk factors (Figure 1). Specifically, the LDL label target population was men $\geq$ 45 years old or women $\geq$ 55 years old, with an LDL cholesterol between 130 and 170 mg/dL, and one or more additional risk factors of hypertension, family history, smoking or low HDL. The total cholesterol label included the same age criterion as the LDL label and specified total cholesterol between 200 and 240 mg/dL. The total cholesterol label also included criteria that women have an HDL cholesterol less than 60 mg/dL and one or more additional risk factors as listed above for the LDL label. For the total cholesterol label men need only meet the age and total cholesterol criteria to be label compliant.

Both labels instructed the consumer that they should not use the drug if they had characteristics that put them at increased risk for adverse events from lovastatin based on their own health history or if their clinical status suggested a need for more intensive cholesterol lowering (Table 1). Drug interactions were written in broad categories to improve consumer recognition (for example, "antifungals" rather than "ketoconazole"). In these cases, the label instructed the consumer not to use the drug before discussing the situation with their physician or pharmacist. The label also indicated that women with an HDL of 60 mg/dL or higher should discuss the use of the drug with their physician due to their probable low absolute cardiovascular risk. Absolute contraindications, identified as "Do not use" on the label, contraindicated use by consumers who were allergic to lovastatin, were currently pregnant or breast feeding or thought they may become pregnant. The remainder of the warnings on the label were considered relative contraindications as they specified that the consumer should not use unless they talked with their physician or (in the case of drug interactions) pharmacist first.

Patient recruitment and study events

Participants were recruited using mass market advertising to attract a diverse population with concern about their cholesterol. No label information was included in the ads, although consumers were told that they should know their cholesterol numbers. Interested consumers were told to call a toll free number for an appointment.

Potential participants who called the toll free number were told they might have the opportunity to purchase ($19.99 for a 45 day supply) a drug currently available only by prescription. Interested callers were given an appointment at a study site in their area. Callers were only excluded at this stage if they could not read and understand English, were under 18 years old, had previously participated in a similar study, were a physician or pharmacist, or were referred to the study by another study participant.

When participants arrived at the study site they were given a proposed OTC lovastatin carton with either the LDL or total cholesterol self-selection algorithm. Assignment to label cohorts was made on an alternating basis stratified by gender and site. At each site the participant had the opportunity to ask for a cholesterol test, but participants were not prompted to obtain the test. After they had inspected the label, each subject was asked "Based on this label, is this product appropriate for you to use right now or not?" The response to this question was recorded as the self-assessment decision. After they responded to this question they were asked "Would you like to pay for this right now for your own use or put it back in the display?" This response was recorded as the purchase decision.

After all participant decisions had been made and recorded, complete demographic information and a medical history were obtained. All participants also had blood drawn to determine their actual lipid profiles. Participants who self-assessed "Yes" despite being ineligible based on label criteria were asked scripted open-ended questions to discern the basis for their incorrect answer. Similarly, participants who self-assessed "Yes" but did not purchase were asked open-ended questions to understand the basis for this apparently inconsistent decision making.

Data analysis

The study was run to accrue approximately 750 consumers evaluating each label. This was deemed sufficient to allow meaningful point estimates for the relevant consumer behaviors. No formal pre-specified hypotheses were incorporated into the protocol and thus all statistics are descriptive.

Demographic information is tabulated as means, medians, ranges and standard deviations, as indicated. Framingham risk scores were calculated using standard methodologies [17]. Self-assessment decisions were tabulated as "Yes", "No" or "Other". The "Other" category included responses such as "I need to discuss this with my doctor" or other indeterminate answers. Purchase decisions were categorized as "Yes" or "No".

Not all data elements were available for all study participants due to missing data from sites or incomplete participation by participants. Thus the total "N" for different aspects of the study will vary. No attempt was made to impute missing data.

RESULTS

Subject disposition and demographics

A total of 5107 individuals called the referral center. Of these, 1528 visited study sites, 1326 made "Yes" or "No" self-assessment decisions (662 with the LDL label and 664 with the total cholesterol label) and 1457 made purchase decisions (732 with the LDL label and 725 with the total cholesterol label). The difference in the number of respondents for the self-assessment and purchase decisions reflects the number of indeterminate ("Other") responses provided to the self-assessment question. The group of participants who reviewed labels and provided decisions represented the evaluator cohort.

The mean age of the 1326 participants for whom self-assessment decisions could be evaluated was 52 years (range 18 to 86), 48.6 % were male, 61.4% were white and 13.7% were of low health literacy based on a REALM score of six or more (Table 2). The demographics of the group for whom purchase decisions were recorded were similar (Table 2). There were no meaningful

demographic differences in the cohort evaluating the LDL label as compared with those who evaluated the total cholesterol label version (data not shown).

Self assessment based on label criteria for OTC lovastatin use based on age, lipids and cardiovascular history

The participants were provided with a proposed OTC carton whose label contained a specific algorithm for self-selection based on age, lipid profile and other cardiovascular risk factors (Figure 1). Of the 662 participants who evaluated the LDL label, 214 (32%) said the drug was appropriate for them, while 242 (36%) of the 664 participants who evaluated the total cholesterol carton responded "Yes". Focusing on those participants who indicated that the drug was appropriate for them after evaluating the LDL label, 82% met the age criterion, 36% met the LDL criterion, and 82% had one or more of the additional cardiovascular risk factors included on the label (Table 3). For the four criteria on the total cholesterol label, 85% of those who self-assessed "Yes" met the age criterion, 50% the total cholesterol criterion, 75% had at least one additional risk factor (applicable to women only) and 55% met the HDL cholesterol criterion (applicable to women only). When all these criteria were combined, 26 % of participants using the LDL label and 37 % of those using the total cholesterol label who self selected "Yes" strictly met all criteria for self-management as per the label algorithm. Thus, the total cholesterol label was associated with a numerical improvement in correct self assessment when compared with the LDL label.

Consumers found self-assessment within the narrow range of lipid values on the label challenging. To better understand the lipid profiles of those consumers who self-assessed as "Yes", the distribution of LDL and total cholesterol values in these cohorts was examined (Figure 2). As can be seen, for both the LDL (Figure 2A) and total cholesterol (Figure 2B) label self-assessment "Yes" groups, the lipid values were typically close to the target range. For example, an additional 11 % and 17 % of consumers who self-assessed "Yes" were within 20 mg/dL of the label specified LDL and total cholesterol ranges, respectively.

The above results are based on the participants' reported lipid values as these would have been the basis of their self-selection decisions in the marketplace. Thus, it is important to assess how these self-reported lipid values compared to lipid concentrations measured at the site. Reported LDL or total cholesterol concentrations were compared with measured concentrations in bands corresponding to label criteria, and bands above and below these criteria: < 130 mg/dL, 130-170 mg/dL and > 170 mg/dL for LDL, and < 200 mg/dL, 200-240 mg/dL and >240 mg/dl for total cholesterol (Tables 4A and 4B). Of those evaluating the LDL label, 76% of the participants reported LDL concentrations corresponding to the correct band based on their measured value, with 79% concordance in the case of the total cholesterol evaluators.

Self-selection by women under the age of 55

A total of 377 women under the age of 55 years evaluated one of the two proposed OTC lovastatin labels, and 42 (11.1 %) indicated that the drug was appropriate for them (13.1 % using the LDL label, 9.0% using the total cholesterol label). Overall, 12.4% of the women under age 55 years in SELECT made an affirmative purchase decision. This compares with 23.5% of the women under 55 years of age who evaluated the drug in CUSTOM and elected to purchase [16]. Of the total of 456 SELECT participants who self-assessed that OTC lovastatin was appropriate for them, 9.2% were women under the age of 55 years. In SELECT, 5.3% of those who indicated they would purchase the drug were women under the age of 55 years as compared with 15% of the CUSTOM user cohort. Of the participants who self-assessed "Yes" in SELECT, 4.6% were women between the ages of 50 and 54, 2.9% were women between the ages of 40 and 49, and 1.7% were women younger than 40 years. When asked why they thought OTC lovastatin was appropriate for them even though they were too young, common answers were that they wanted to lower their cholesterol, that they had a positive family history, or that their age was close.

Self-selection by women of child bearing potential or who are pregnant

The evaluator cohort included four women who were pregnant. One of these women indicated the drug was appropriate for her use, but all answered "No" to the purchase decision. Open ended questioning of the pregnant participant who self-assessed "Yes" indicated that she understood that she was not to use the drug but misunderstood the intent of the self-assessment question as evidenced by her "No" purchase decision.

Twenty-two women responded "Yes" when asked if they thought they may become pregnant. Only two indicated that the drug was appropriate for their use, but all said "No" to the purchase decision. Open-ended questioning of these two participants indicated they may not have understood the self –assessment question. One additional participant was breast feeding, and indicated that the drug was not appropriate for her use and said "no" to the purchase decision.

Participants with calculated low cardiovascular risk

Framingham 10-year cardiovascular risk estimates were calculated for all participants. However, the participants were unaware of their risk score and thus did not base any decisions on the score. In examining the risk profiles, the LDL and total cholesterol label cohorts were combined as there were no meaningful differences between the two groups. The self-assessment "Yes" group included 25% with 10-year risks under 5%, 41.5% with 5-25% risk, and 2.4% with risks above 25% (Figure 3). The remaining 31.4% included participants with known coronary heart disease, stroke, diabetes, currently taking lipid lowering therapy, or missing data, precluding calculation of a Framingham risk score. Of note, of the participants with preexisting diabetes, coronary disease or stroke, or with high Framingham risk, approximately 70% were on no lipid therapy when entered into SELECT. Interestingly, 22% of the 113 participants who self-assessed "Yes" and were deemed by Framingham calculations to be at low risk were fully compliant with the label's age, risk factor, and lipid criteria. These were primarily women 55-65 years of age with one or two label-defined risk factors. This stratum with 10-year risk below 5% also included most of the women under 55 years of age.

Purchase decisions

Purchase and self-assessment decisions were largely concordant (kappa measure of agreement yields $\kappa = 0.71$ with 95% confidence interval 0.67-0.75). As noted above for the pregnant patient who self-assessed "Yes", the exceptions tended to reflect participants' greater caution with purchasing a drug than when indicating it was "appropriate" or confusion over the intent of the self-assessment question. For example, the two most common reasons to not purchase were a desire to speak with their doctor before using, and recognition by the participant that they did not meet criteria for use.

Safety-related self-selection

The evaluator cohort included many participants with label contraindications for self-management with OTC lovastatin. Consumers with these conditions were effectively discouraged from self-selection by the label (Table 5). Those few evaluators who incorrectly indicated that the drug was appropriate for them frequently indicated that they would discuss the drug with their physician before using, including all four evaluators with potential drug interactions.

Of note, 86 participants who self-assessed "Yes" were currently on lipid lowering medications and 58 indicated that they would purchase the drug. Thirty-one (36%) of those who self-assessed "Yes" and 22 (38%) of those who indicated that they would buy the drug also indicated that they would talk with their doctor before using. Thirty-two (55%) of the 58 participants on lipid lowering therapy who wanted to purchase the drug indicated that they would use the OTC drug as a substitute for their existing therapy.

DISCUSSION

Clinical research data are critical to informing decision making as to whether statins can be used safely and effectively in the OTC setting. Previous work has demonstrated that consumers who were interested in purchasing an OTC statin were capable of self-managing their treatment, including having knowledge of their cholesterol concentrations, heeding warnings against use based on personal health characteristics that would be associated with increased risk, and adhering to treatment over time [13, 14]. SELECT builds on this data to show that an improved label facilitated appropriate self-selection based on a label algorithm designed to reflect NCEP primary prevention criteria while decreasing inappropriate use by women under the age of 55 years or who are pregnant or may become pregnant.

As was the case in CUSTOM [13], participants were able to self-select for OTC lovastatin use based on an algorithm incorporating age, lipid profile and other risk factors (Table 3). This algorithm was designed to mimic NCEP guidelines for primary prevention treatment with statins, and has been endorsed as an appropriate OTC target population by the FDA's Nonprescription Drug and Endocrine and Metabolic Drug Advisory Committees [16]. It was hypothesized that consumers might be more familiar with their total cholesterol concentrations than their LDL cholesterol concentrations, and that a total cholesterol-based algorithm might improve consumer utility. SELECT demonstrated that this might be the case, with a 39% improvement in compliance with the label lipid criteria on the total cholesterol label as compared with the LDL label and a 50% improvement in compliance with all of the benefit self selection criteria, despite four criteria being present on the total cholesterol label versus three on the LDL label (Table 3). This may be important, as the lipid range was the most challenging of the three elements for consumers. Nonetheless, using either label, the overall lipid profile of participants who self-assessed "Yes" was largely consistent with a primary prevention target population (Figure 2). The lipid profiles are also consistent with the label range's intent to provide a surrogate for cardiovascular risk in the context of NCEP recommendations, rather than to define absolute cut-offs for use. Importantly, as previously demonstrated in CUSTOM [14], self-reported LDL or total cholesterol values in SELECT were in good agreement with those actually measured (Table 4), with very few errors where the self-report was inaccurate towards the extremes (for example self reported low, LDL <130 mg/dL, but was actually high, >170 mg/dL).

Despite the modeling of the label algorithm on NCEP criteria and the ability of participants to apply the algorithm to their condition, the self-assessment "Yes" cohort included many consumers with estimated Framingham 10-year cardiovascular risk of less than 5%. Framingham criteria provide low risk estimates for some label-compliant individuals. For example, a 55 year old woman with a total cholesterol of 220 mg/dL, an HDL cholesterol of 50 mg/dL, and who smokes has an estimated risk of less than 5%. It has been suggested that the Framingham risk calculation may underestimate rates of atherosclerosis [18] and cardiovascular events in women [19]. This has resulted in guidelines that recommend increased flexibility when NCEP criteria are applied to women [20], consistent with the proposed label. Importantly, consumers whose age, lipid and risk factor profiles matched the tested OTC label were included in the landmark primary prevention trial AFCAPS/TexCAPS, which established the benefit of primary prevention with statins [21,22]. Thus, the self-selection for OTC treatment by label-compliant consumers with relatively low absolute risk should be viewed in the context of the inherent flexibility in the published guidelines and the risk reduction that these individuals will likely receive.

A major focus after CUSTOM was to reduce self-selection by women under the age of 55 years. Thus, the labels used in SELECT featured the age criteria on the front panel as well as in the back panel algorithm with increased clarity. These modifications appeared to be effective, as almost 90% of the evaluators who were women under 55 years indicated that the product was not appropriate for them, as compared with 75% of the general evaluator cohort. Direct comparisons with CUSTOM are limited as CUSTOM only recorded the participant's actual purchase and not a distinct self-assessment decision. However, the contribution of women under 55 years old to the

purchase cohort was decreased to 5.3% in SELECT as compared with 15% in CUSTOM. [16]. The new label was also very effective in discouraging use by women who were pregnant or who thought they may become pregnant.

Consumers at higher cardiovascular risk sometimes self-selected for OTC use, despite the label directions to seek professional assistance due to the need for more intensive therapy. As was observed in CUSTOM, in many cases the desire to use the OTC statin appeared to be driven by the fact that it was the only drug treatment acceptable to the consumer and was not a substitute for intensive, supervised care. In such cases, the OTC statin would be of substantial benefit to the consumer. Nonetheless, the potential under-treatment of higher risk patients if OTC statins are available remains an important concern [10,11,16]. Analyses suggest that diversion of patients from optimal care is unlikely to offset the individual and public health benefits from the broader use of statins associated with OTC statin availability [15]. In the case of SELECT, of the participants who self-assessed "Yes" despite having diabetes, coronary heart disease or a history of stroke, two-thirds were on no lipid-lowering therapy. Similarly, of those without these conditions but a calculated Framingham risk of greater than 25%, 90% were not on treatment. Thus, OTC access to lovastatin may bridge the treatment gap for these higher risk patients and, as in CUSTOM [13], ultimately direct them to proper supervised care.

As in CUSTOM, violations of major safety warnings were rare and unlikely to represent risks to the consumer (Table 4). Some consumers self-selected for use despite already being on lipid lowering therapy. In part this may reflect the artificial setting of a clinical trial, but nonetheless most of these participants on lipid lowering therapy indicated that they would talk to their doctor before using the OTC drug and/or would substitute the OTC drug for their existing medication.

Results from SELECT demonstrate improved self-selection in several areas and preservation of appropriate decision making in remaining areas when compared with CUSTOM. Importantly, SELECT offered consumers less guidance on self-selection, with materials limited to only the proposed product carton and label. In contrast, consumers in CUSTOM had access to additional sources of information that would be available in the OTC marketplace, including decision making tools such as information tear pads and a display based "decision wheel" that incorporated the self-selection algorithm. Thus, SELECT may under-estimate the positive impact of the label changes made, as well as the effectiveness of consumer decision making when all resources of the actual OTC environment are available.

Despite the general concordance, some participants who self-assessed "Yes" for OTC lovastatin subsequently responded "No" to the purchase question. Further questioning of these participants revealed in many cases that they understood that they shouldn't use the product, but that they were confused by the intent of the self-assessment question. This suggests that the purchase decision endpoint may be more relevant than the self-assessment question to understanding true potential marketplace behaviors. The purchase decision also seems most relevant because a drug can only harm or benefit a consumer if it purchased and used. Another advantage of focusing on the purchase decision is its absolutely binary nature (the participant either purchases or doesn't). In contrast, the self-assessment question may elicit ambiguous responses despite instructions for a Yes/No response. In SELECT, approximately 10% of the self-assessment responses could only be categorized as "Other".

Thus, the results of SELECT, when combined with those from CUSTOM, provide evidence that consumers can safely and appropriately use OTC lovastatin in an unsupervised setting. OTC availability of statins has the potential to substantively improve public health [6,15].

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Table 1. Label directions for self-selection on the tested LDL label. Wording is that used on the LDL label. Analogous statements appeared on the total cholesterol label, modified based on the lipid criteria used.

Do not use

- If you are allergic to lovastatin
- If pregnant or breast-feeding, or think you may become pregnant, do not use. This product may cause problems in the unborn child.

Ask a doctor before use if you

- Are taking prescription cholesterol medicines. Do not substitute. This product is probably not strong enough for you.
- Have LDL "bad" cholesterol 171 to 400. You are at higher risk for heart disease.
- Are a woman under age 55 or a man under age 45. You may be at lower risk for heart disease.
- Have liver disease
- Have had heart disease
- Have had a stroke
- Have diabetes

Ask a doctor or pharmacist before use if you are

- Unsure of your cholesterol numbers or have not had a fasting cholesterol test within the last year
- Taking any of the following, as certain drugs or foods can cause interactions:
    - cholesterol medicines
    - oral antibiotics
    - oral antifungals
    - drugs for irregular heart beat
    - HIV protease inhibitors
    - cyclosporine (immune suppressant)
    - nefazodone (antidepressant)
    - large quantities of grapefruit juice (more than 1 quart daily)

Table 2. Demographics of the study participants making self-selection decisions. Low health literacy was defined as a REALM score of 6 or more.

Demographic	Self-Assessment (N=1326)	Purchase decision (N=1457)
Age (years)		
Mean	51.8	52.2
Median	52.0	52.0
Range	18-86	18-86
Gender (%)		
Male	48.6%	48.1%
Female	51.4%	51.9%
Racial origins (%)		
Caucasian	61.4%	62.9%
Black	25.5%	24.5%
Hispanic	7.4%	7.3%
Asian	2.2%	2.1%
Native American	1.2%	1.1%
Other	2.3%	2.2%
Health literacy (%)		
Low literacy	13.7%	13.5%
Non-low literacy	86.3%	86.5%

Table 3. Use of the self-selection algorithm. Responses for participants who indicated that OTC lovastatin was appropriate for their use (self-assessment) were analyzed for correctness at each step of the self-selection algorithm (see Methods and Figure 1). The percent correct for each criterion for each label format is shown. The correctness of the lipid criterion was based on the participant's self-reported lipid values. Note that the "Additional risk factor" and "HDL cholesterol" criteria applied only to women for the total cholesterol label, and the percentages refer to the percentage of women (n = 97) who self-assessed "Yes". "All correct" refers to participants who met all listed criteria for the LDL or total cholesterol labels.

Criterion	LDL Label (n = 214)	Total Cholesterol Label (n = 242)
Age	82%	85%
Lipid (LDL or total cholesterol)	36%	50%
Additional risk factor	82%	75%
HDL cholesterol	Not applicable	55%
All correct	26%	37%

Table 4. Agreement between self-reported cholesterol concentrations and measured values. Self-reported LDL or total cholesterol concentrations of evaluators of each of the two labels were compared to the values actually measured at the end of the self-assessment and purchase decision process. Data were grouped by range to facilitate comparison with the label criteria. A. LDL concentrations for those evaluating the LDL label (N = 470), B. Total cholesterol concentrations in those evaluating the total cholesterol label (N = 583). The number of participants in each self-reported vs. measured grouping are shown.

A. Measured LDL cholesterol (mg/dL)

Self-reported LDL cholesterol (mg/dL)	**< 130**	**130-170**	**>170**
<130	141	13	0
130-170	25	127	19
> 170	5	18	90

B. Measured total cholesterol (mg/dL)

Self-reported total cholesterol (mg/dL)	**< 200**	**200-240**	**>240**
<200	116	9	3
200-240	29	152	39
> 240	12	25	192

Table 5. Self-assessment and purchase decisions by participants with label contraindications. Data are from the participants who provided self-assessment decisions or purchase decisions. The number of evaluators for each decision with the condition is shown in the denominator and the number making a "Yes" decision in the numerator, with the percentage making a "Yes" decision shown in parenethesis.

Label warning	**Self-assessment**	**Purchase**
Pregnant or breast feeding	1/5 (20%)	0/5 (0%)
May become pregnant	2/22 (9%)	0/22 (0%)
Allergy to lovastatin	0/11 (0%)	0/11 (0%)
Potentially interacting medication	4/21 (19.1%)	3/21 (14%)
Liver disease	3/39 (7.7%)	3/39 (7.7%)
Currently taking lipid lowering medication	86/261 (33%)	58/259 (22%)

Figure legends

Figure 1. Label directions for self-selection based on cardiovascular risk. The LDL (A) and total cholesterol (B) labels are shown.

Figure 2. Distribution of LDL (Panel A) and total cholesterol (Panel B) concentrations for participants who self-assessed "Yes" for each of the two labels. Lipid values are broken into discrete 10 mg/dL ranges for ease of presentation. Panel A includes 136 of the 214 participants who evaluated the LDL label and self-assessed "Yes", as 78 participants did not know their LDL cholesterol or gave a general range in response to the question. Similarly, panel B includes 191 of the 242 participants who evaluated the total cholesterol label and self-assessed "Yes".

Figure 3. 10-Year cardiovascular risk estimates for participants self-assessing that OTC lovastatin was appropriate for them. LDL and total cholesterol label cohorts are combined with data available for 456 of the 494 self-selection "yes" responders. The numbers of 313 participants with self-assessment "Yes" with 10-years risks less than 5%, between 5% and 10%, 10% and 20%, 20% and 25% and above 25% are shown. Excluded were 143 participants who had a history of coronary artery disease, stroke or diabetes, or who were taking lipid lowering medications, or who were missing data required to calculate their Framingham risk.

Figure 1A

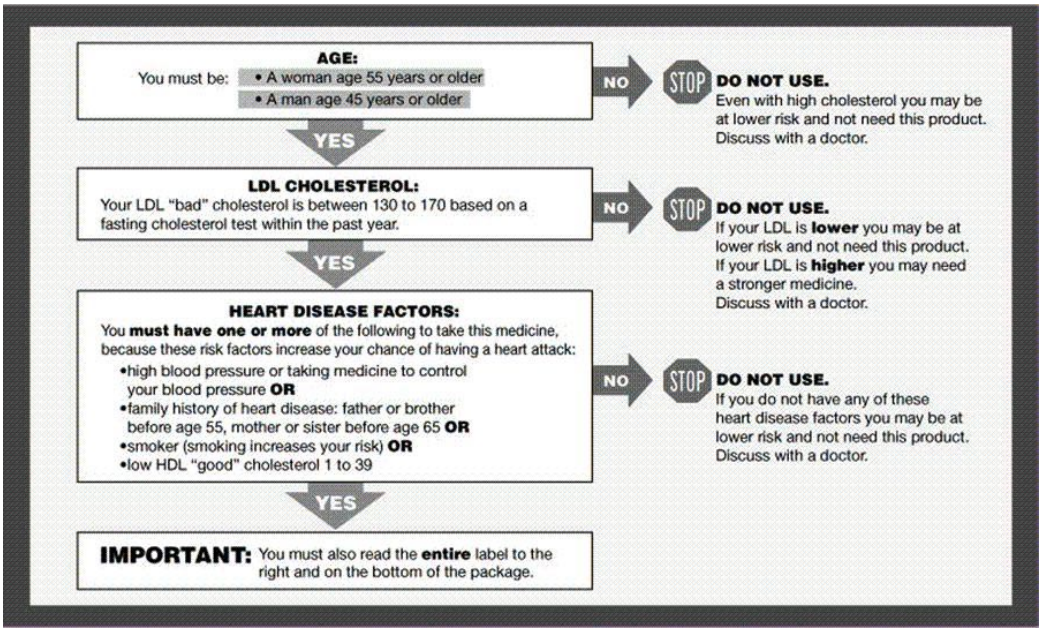

AGE:
You must be:
• A woman age 55 years or older
• A man age 45 years or older
NO
STOP
DO NOT USE.
Even with high cholesterol you may be at lower risk and not need this product. Discuss with a doctor.
YES
LDL CHOLESTEROL:
Your LDL "bad" cholesterol is between 130 to 170 based on a fasting cholesterol test within the past year.
NO
STOP
DO NOT USE.
If your LDL is lower you may be at lower risk and not need this product.
If your LDL is higher you may need a stronger medicine.
Discuss with a doctor.
YES
HEART DISEASE FACTORS:
You must have one or more of the following to take this medicine, because these risk factors increase your chance of having a heart attack:
•high blood pressure or taking medicine to control your blood pressure OR
•family history of heart disease: father or brother before age 55, mother or sister before age 65 OR
•smoker (smoking increases your risk) OR
•low HDL "good" cholesterol 1 to 39
NO
STOP
DO NOT USE.
If you do not have any of these heart disease factors you may be at lower risk and not need this product.
Discuss with a doctor.
YES
IMPORTANT: You must also read the entire label to the right and on the bottom of the package.

Figure 1B

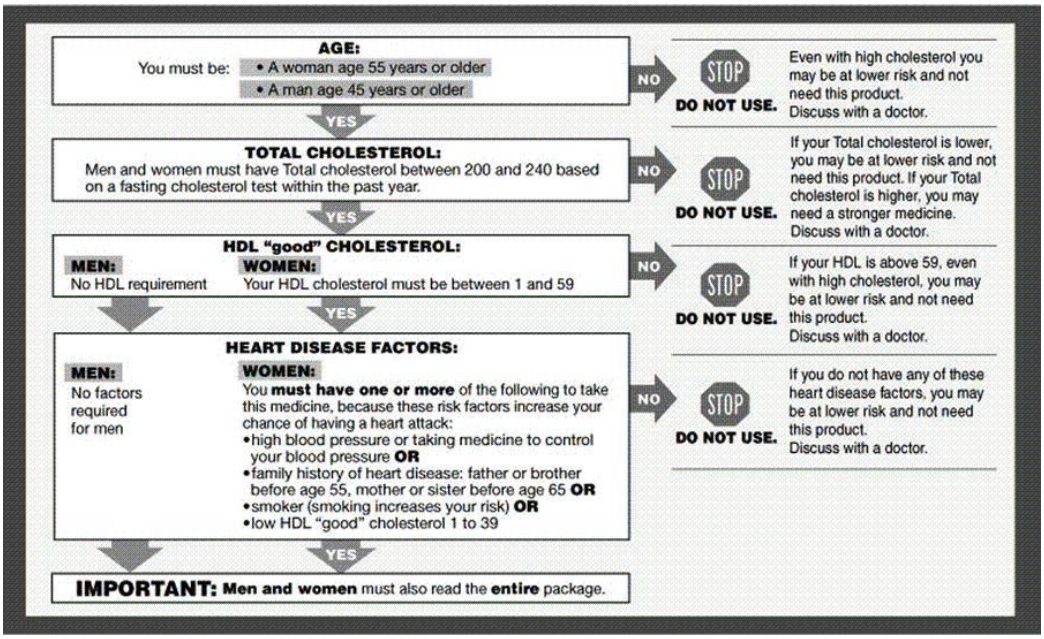

AGE:
You must be:
• A woman age 55 years or older
• A man age 45 years or older
NO
STOP
DO NOT USE.
Even with high cholesterol you may be at lower risk and not need this product. Discuss with a doctor.
YES
TOTAL CHOLESTEROL:
Men and women must have Total cholesterol between 200 and 240 based on a fasting cholesterol test within the past year.
NO
STOP
DO NOT USE.
If your Total cholesterol is lower, you may be at lower risk and not need this product. If your Total cholesterol is higher, you may need a stronger medicine. Discuss with a doctor.
YES
HDL "good" CHOLESTEROL:
MEN:
No HDL requirement
WOMEN:
Your HDL cholesterol must be between 1 and 59
NO
STOP
DO NOT USE.
If your HDL is above 59, even with high cholesterol, you may be at lower risk and not need this product. Discuss with a doctor.
YES
HEART DISEASE FACTORS:
MEN:
No factors required for men
WOMEN:
You must have one or more of the following to take this medicine, because these risk factors increase your chance of having a heart attack:
•high blood pressure or taking medicine to control your blood pressure OR
•family history of heart disease: father or brother before age 55, mother or sister before age 65 OR
•smoker (smoking increases your risk) OR
•low HDL "good" cholesterol 1 to 39
NO
STOP
DO NOT USE.
If you do not have any of these heart disease factors, you may be at lower risk and not need this product. Discuss with a doctor.
YES
IMPORTANT: Men and women must also read the entire package.

Figure 2A

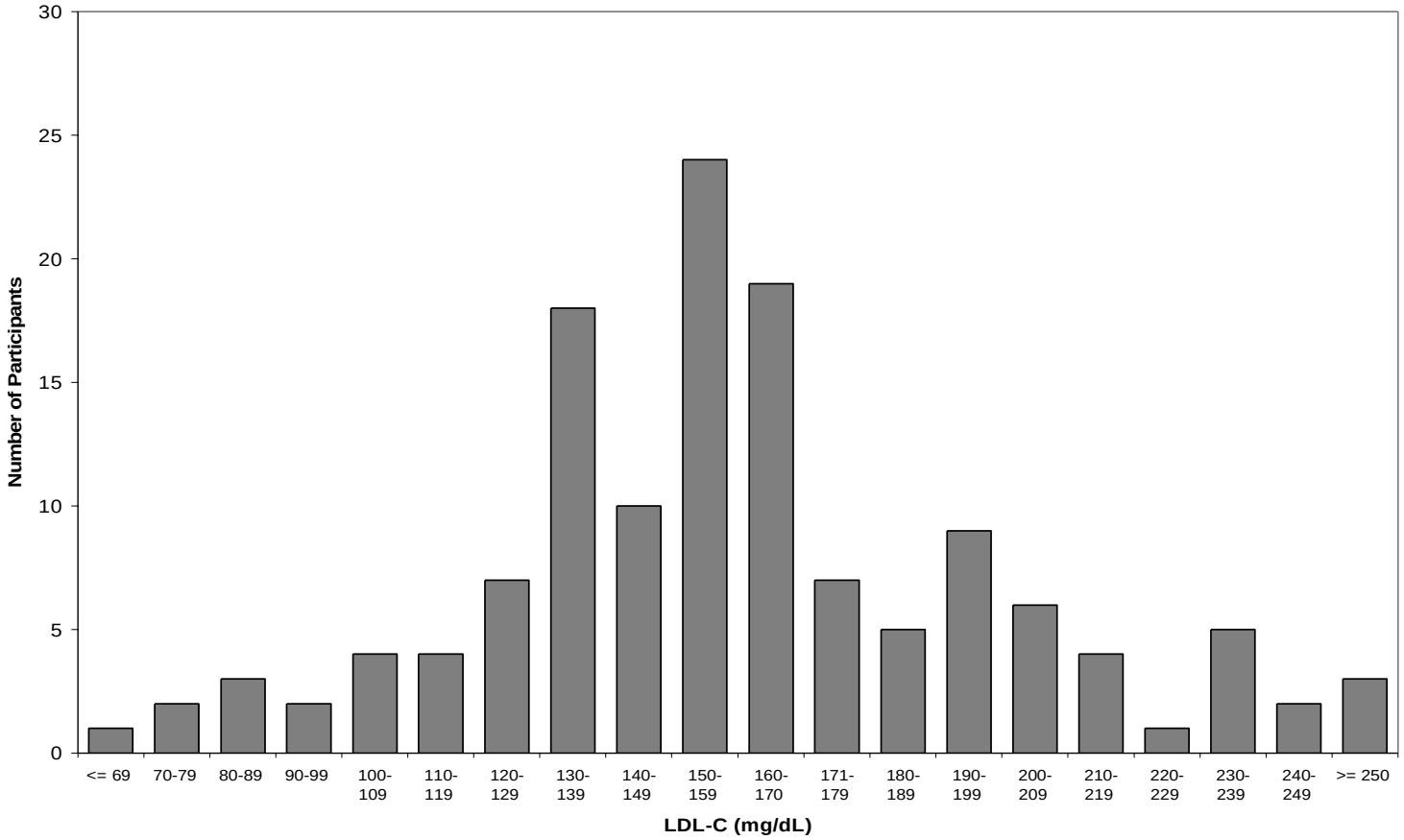

30
25
20
15
10
5
0
Number of Participants
<= 69
70-79
80-89
90-99
100-109
110-119
120-129
130-139
140-149
150-159
160-170
171-179
180-189
190-199
200-209
210-219
220-229
230-239
240-249
>= 250
LDL-C (mg/dL)

Figure 2B

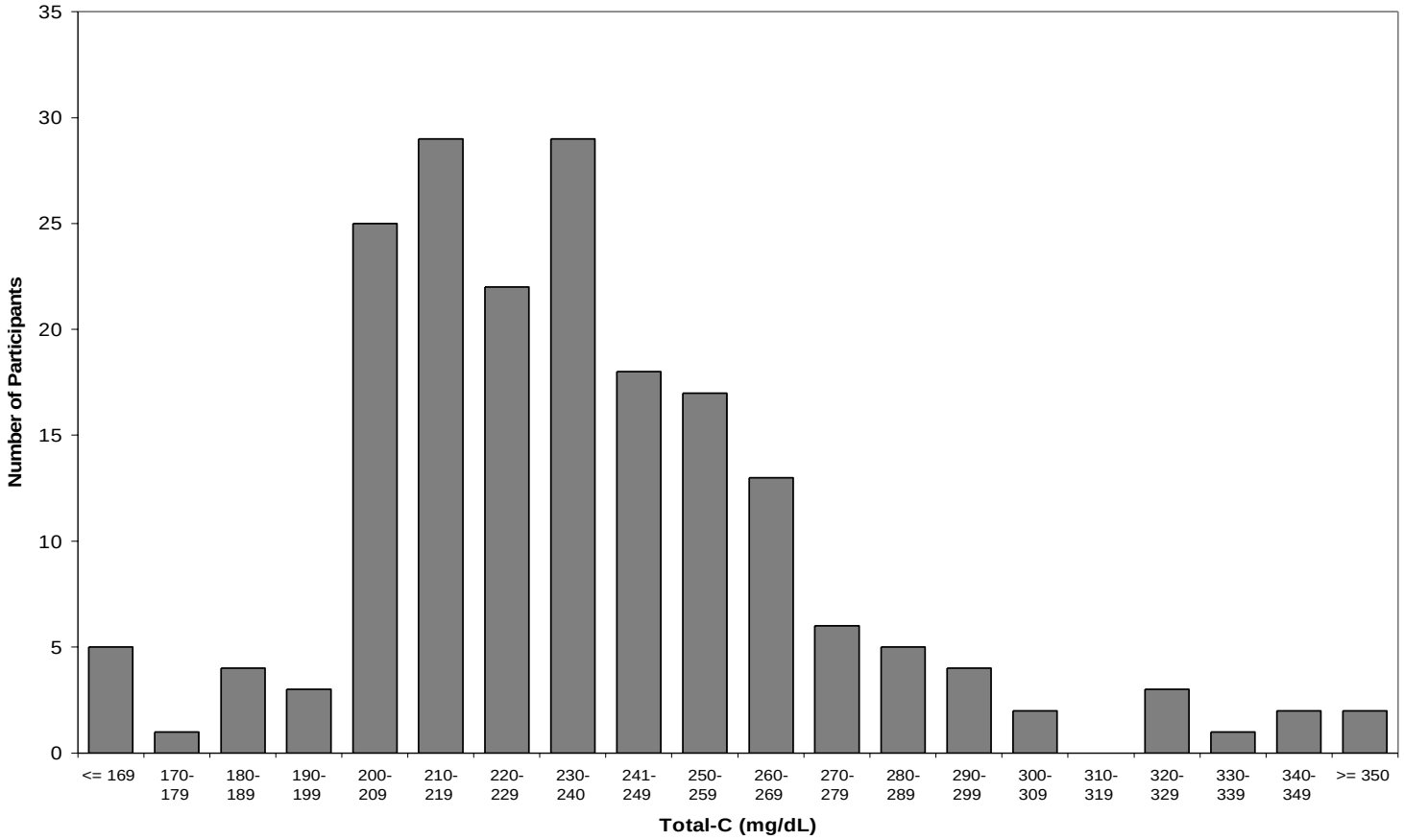
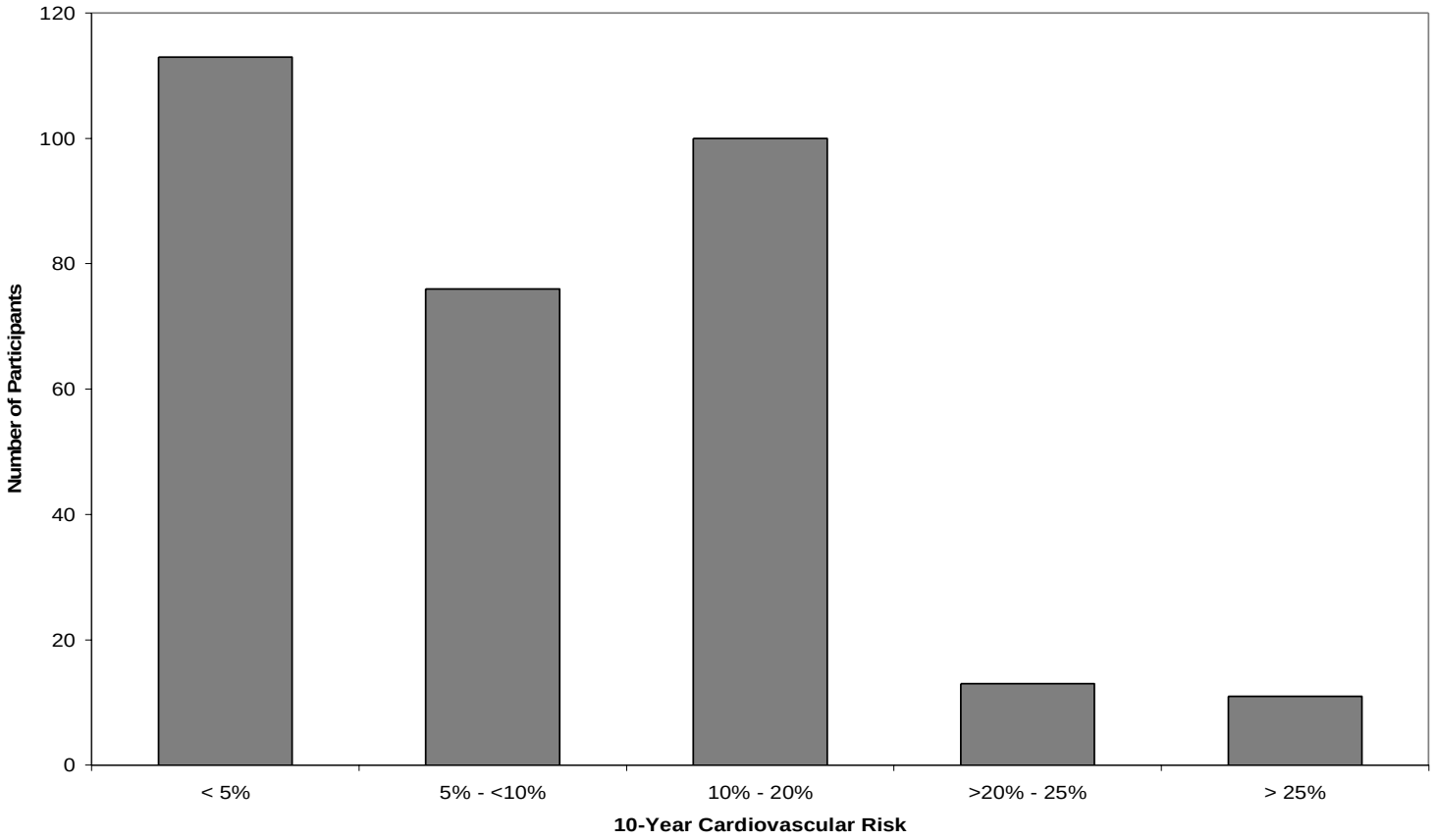

35
30
25
20
15
10
5
0
Number of Participants
<= 169
170-179
180-189
190-199
200-209
210-219
220-229
230-240
241-249
250-259
260-269
270-279
280-289
290-299
300-309
310-319
320-329
330-339
340-349
>= 350
Total-C (mg/dL)

Figure 3


120
100
80
60
40
20
0
Number of Participants
< 5%
5% - <10%
10% - 20%
>20% - 25%
> 25%
10-Year Cardiovascular Risk

C. MEVACOR DAILY SELF-MANAGEMENT SYSTEM AND MARKETING PLANS

C. MEVACOR™ Daily SELF MANAGEMENT SYSTEM AND MARKETING PLANS

1. Introduction

Merck and GSK are highly committed to ensuring that proper consumer behavior will be the cornerstone of the MEVACOR™ Daily cholesterol treatment program. This commitment includes the development of the MEVACOR™ Daily Self Management System, a comprehensive approach to ensuring proper consumer behavior in lowering cholesterol.

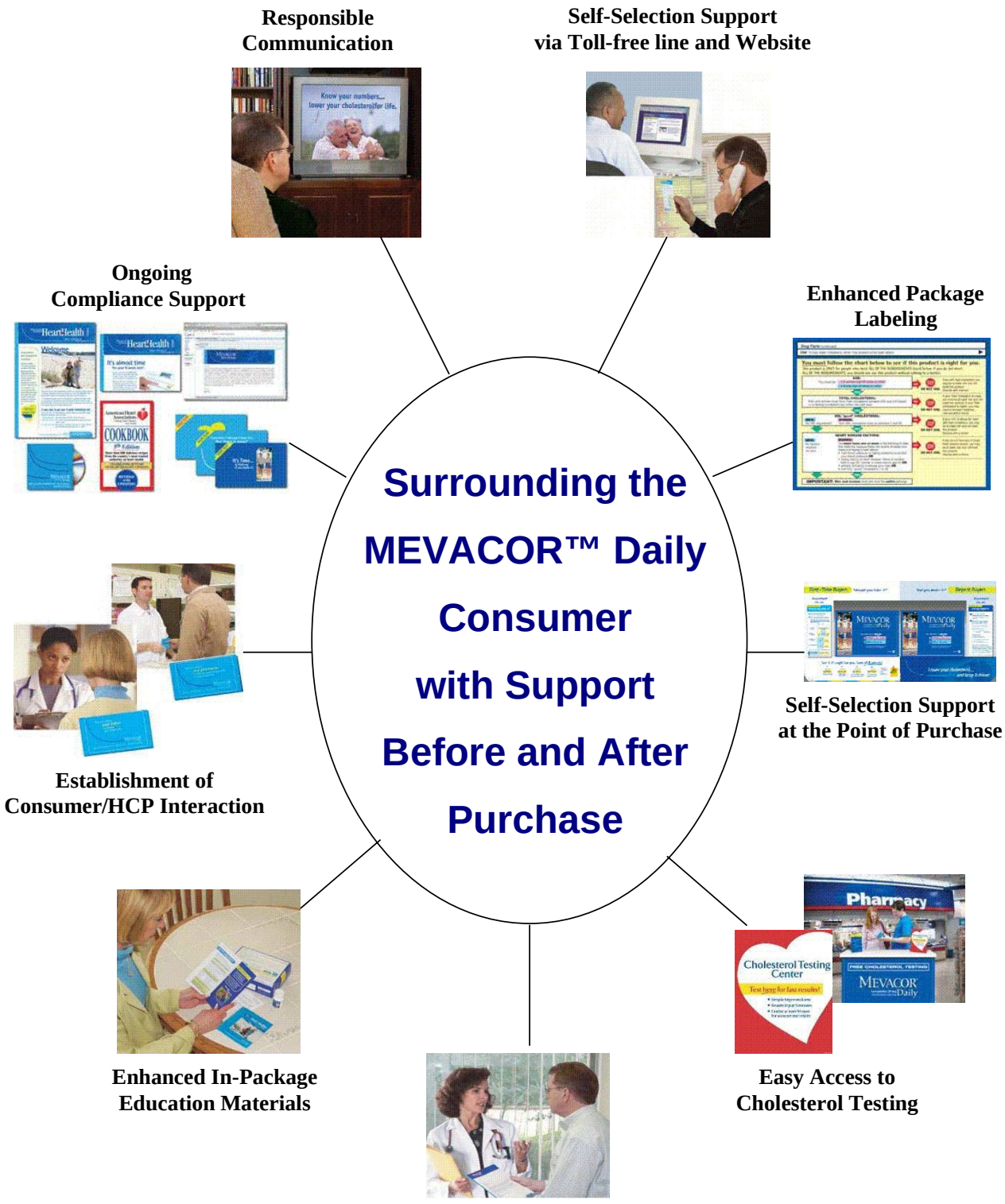
The system consists of multiple components, most of which have been tested and demonstrated to be successful in the CUSTOM Actual Use study. To ensure these results translate into the real-world setting, We are committed to an extensive in-market monitoring program that will provide an accurate picture of consumer behavior including self-selection, usage patterns, and de-selection. Results from the in-market monitoring program will be shared with FDA on a timely basis and adjustments will be made to the Self Management System, if necessary.

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™ Daily Self Management System 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™ Daily
- 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 all touch points: internet, toll-free number, media and the retail point of purchase
- Direct appropriate consumer behavior through enhanced labeling and educational materials inside the package and on-line
- 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™ Daily

Because consumer research has indicated that not every consumer will choose to take advantage of every tool provided, the System has been designed to provide multiple consistent messages about the appropriate use of MEVACOR™ Daily. The expected result of this comprehensive System design is that the vast majority of consumers will utilize at least some of the available tools, and that all consumers will have access to the same key support messages.


Responsible Communication
Know your numbers... lower your cholesterolfor life.
Self-Selection Support via Toll-free line and Website
Ongoing Compliance Support
Heart Health
COOKBOOK
Enhanced Package Labeling
Surrounding the MEVACOR™ Daily Consumer with Support Before and After Purchase
Establishment of Consumer/HCP Interaction
Self-Selection Support at the Point of Purchase
Enhanced In-Package Education Materials
Pharmacy
Cholesterol Testing Center
Test here for fast results!
MEVACOR
Easy Access to Cholesterol Testing
High CHD Risk Referral

2. Self Management System Tools and Marketplace Implementation

2.1. Usage Management Tools Included in Self -Management System

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

Merck and GSK will limit the distribution of MEVACOR™ Daily 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 (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 support staff on MEVACOR™ Daily and appropriate consumer use of the product
- In-store consumer educational materials 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
- Sponsorship of cholesterol screening events at select retail pharmacies and other major consumer venues

In Retail Stores with Pharmacies Only

In-store Educational Materials

Pre-Purchase Consumer Assistance

Cholesterol Screening at Retail

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

Merck and GSK are committed to promoting MEVACOR™ Daily 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™ Daily
- All consumer communications will encourage interaction with 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

2.1.3 Pre-Purchase Consumer Assistance Program

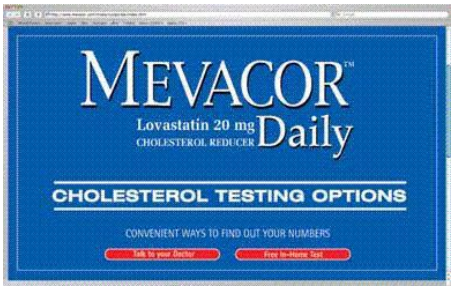
Realizing the importance of proper self-selection, Merck has developed with input from GSK a Pre-Purchase Consumer Assistance Program to assist consumers with the self-selection process. Using a toll-free hotline or website, consumers will be taken through selection criteria in a simple, easy to understand,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

Pre-Purchase Assistance via Web, Pharmacist & Physician, and Phone

2.1.4 Cholesterol Testing Referral Service

With the availability of MEVACOR™ Daily, 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™ Daily Self Management System will include information on how consumers can get an initial test and obtain pre-treatment cholesterol test results. This material 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, Merck and GSK commit to sponsor periodic convenient screening events (e.g., at retail pharmacies), and work to establish partnerships with testing and device companies to communicate clear test result interpretations.



Online Cholesterol Testing Referral Service

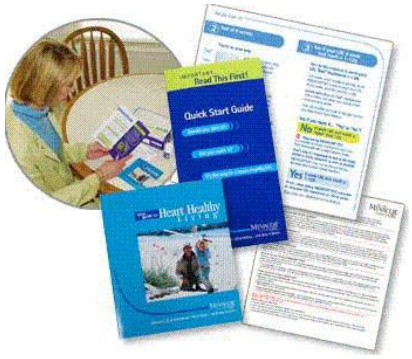
Cholesterol Testing Events

2.1.5 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
- Notification cards consumers can share with their doctor and pharmacist informing them that they are using MEVACOR™ Daily
- 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 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, including the second month of MEVACOR™ Daily free
- Informative package insert in Question and Answer format
- "Refrigerator message magnet" which serves as an additional safety reminder to consumers on muscle pain symptoms and potential drug interactions

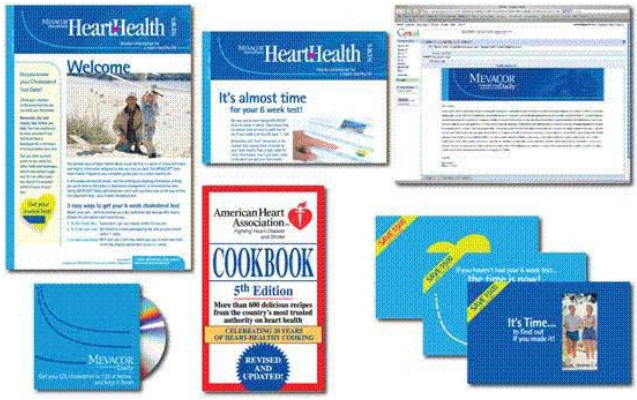


In-Package Education Materials

2.1.6 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™ Daily Post-Purchase Consumer Assistance Program. The multi-faceted Post-Purchase Program will provide communication options 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™ Daily
- Link to MEVACOR™ Daily Cholesterol Testing Referral Service
- Scheduled series of communications (i.e., newsletters, postcards)



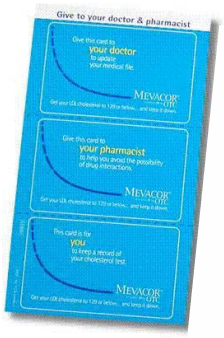
Post-Purchase Compliance Education and Support

2.1.7 Healthcare Professional Collaborative Care Messages

Although healthcare professional consultation is not a requirement for product use, the MEVACOR™ Daily 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™ Daily 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 consumer consultation with trained specialists managed by a healthcare professional. Merck and GSK will also work to establish:

- 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 Institute of Health) to coordinate messages and disseminate materials to educate consumers on cholesterol management

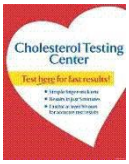


Pharmacist and Physician Notification Cards Included in Packaging

2.1.8 High CHD Risk Consumer Identification and Referral Service

As a result of MEVACOR™ Daily availability, we predict that many consumers will contact GSK via the toll-free hotline, or consult with their doctor and/or pharmacist. 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 and choose to contact us, we will recommend, via various messages in package labeling, website and personal communications, that they see their physician for appropriate treatment.

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 High-Risk Individuals

2.1.9 Healthcare Professional Education Programs

In addition, Merck and GSK commit to conducting an education campaign that will involve healthcare professionals to raise awareness and knowledge levels about the diagnosis and treatment of hypercholesterolemia. Particular attention will center on the NCEP - ATP III Treatment Guidelines and determining appropriateness for use of MEVACOR™ Daily according to label directions. The program will include continuing education by certified providers and will be made readily accessible through web sites, toll-free numbers, and made available to State Boards of Pharmacy for their use at various education programs and meetings. We will also work with drug store chains to develop education programs to be disseminated to pharmacists throughout the entire chain's system.

Pharmacist and Physician Educational Kits

3. In-Market Monitoring

Given the potential for MEVACOR™ Daily to be the first statin to switch to OTC, we commit to develop and implement a comprehensive in-market monitoring program to track consumer usage patterns to identify and report to FDA consumer behavior that may compromise appropriate consumer use. We are working with an outside firm (Pinney and Associates) that has experience in developing in-market monitoring programs for some of the more recent Rx-to-OTC switches, including nicotine replacement, Plan B contraceptive, and orlistat for weight loss. The objective of our program is to monitor data about real-world use of MEVACOR™ Daily, including safety, self-selection, consumer interactions with healthcare professionals, cholesterol monitoring, adherence (compliance and persistence) to therapy, and therapeutic lifestyle modifications made while on OTC therapy. If necessary, adjustments will be made to the MEVACOR™ Daily Self-Management System to improve consumer safety and benefit.

To minimize sampling bias in the post-marketing program, we will utilize a combination of complementary approaches designed to reflect actual consumer usage of the product. The primary methodology for data gathering will be the use of various survey techniques and will include longitudinal usage by actual purchasers and users of the product. In addition to collecting information from consumers, we will also conduct surveys with pharmacists to gain their insight into the overall cholesterol reduction program. Data gathered from pharmacists will serve to gauge the impact and effectiveness of pharmacist training programs as well as to assess consumer questions and concerns and the ability of pharmacists to properly address them.

To accurately and objectively analyze the data collected in the in-market monitoring program, Merck and GSK will convene an Expert Advisory Board. The board will be comprised of approximately a half-dozen independent experts from the fields of cardiology, epidemiology, preventive medicine, behavioral medicine, and health communication. The board will initially be convened before launch and will meet on a regular basis after launch with more frequent meetings occurring immediately after launch. The objective of the board will be to review the in-market monitoring data and make recommendations to enhance the Self Management System.

The proposed in-market monitoring program will allow for an accurate picture of actual usage information including self-selection, usage patterns, and de-selection. Merck and GSK commit to monitor, detect, and report in a timely manner (through quarterly NDA reports) to FDA findings regarding consumer behaviors that may be of concern, so that interventions can be made in a timely manner.

D. BENEFIT/RISK ASSESSMENT AND CONCLUSIONS

D. BENEFIT/RISK ASSESSMENT & CONCLUSIONS

1. Introduction

MEVACOR™ Daily is intended for use as primary prevention of CHD by consumers who are at moderately high risk of CHD (10-20% over 10 years), consistent with the NCEP ATP III Guidelines (see Appendix 5). The importance of primary prevention of CHD is well-established and the value of statins, including lovastatin 20 mg, for decreasing cardiac events in this population is accepted. Additionally, persons who are at lower NCEP ATP III risk (less than 10% over 10 years) can still be at significant risk of CHD and treatment with lovastatin has been shown to decrease CHD events in these individuals. The label criteria endorsed by the Advisory Committee and FDA in 2005 are consistent with these Guidelines, although Framingham 10-year risk scores for people meeting these criteria may be less than 5%, especially in women less than 65 years old.

A significant gap currently exists in both the identification and treatment of hypercholesterolemic individuals. MEVACOR™ Daily would help narrow this gap because of:

- Interest by consumers and acceptance by health care providers of increased self-care options.
- A marketing and support campaign designed to increase consumer awareness and appropriate lipid management, including life-style and prescription drug approaches.
- Evidence that therapeutic lifestyle changes will be maintained or improved with the availability of MEVACOR™ Daily.

The availability of MEVACOR™ Daily is expected to increase appropriate consumer interaction with health care providers (as evidenced in CUSTOM), which will also result in consumers being initiated by their physicians on therapeutic lifestyle changes or, when appropriate, on prescription statins. The potential public health impact of MEVACOR™ Daily has been shown to be positive and meaningful when analyzed on the basis of the distribution of Framingham Risk Scores of the consumers actually enrolled in the CUSTOM Study.

The potential risks with use of this product have been appropriately addressed. Key concerns include the potential for myopathy, use by women of childbearing potential, and use by individuals with undiagnosed hepatic disease. The first two of these, myopathy and use by women of childbearing potential (i.e., potential for fetal exposure), have been effectively addressed by the currently proposed Drug Facts and other package material. The third issue, use with undiagnosed hepatic disease, has been addressed through studies that demonstrated minimal hepatic risk in these individuals. Detailed review of the potential benefits and risks of over-the-counter lovastatin is presented below.

2. Benefits

2.1 Primary Prevention

The NCEP ATP IIII Guidelines underscore the importance of primary prevention and state that delaying treatment until a diagnosis of CHD is made will result in persons with CHD presenting with sudden cardiac death or disability. Primary prevention can be separated into short-term and long-term prevention. Long-term prevention is directed at persons not in imminent danger of a major coronary event but who have a high probability of developing CHD sometime during their lives. Short-term prevention is directed at persons who in all probability already have advanced coronary atherosclerosis and who are at high risk of acute coronary syndromes. The ATP III Guidelines recommend a method of assessing short term (10 year) risk which utilizes risk factor counting as well as the Framingham Risk Score. Once the risk level is assessed appropriate treatment can be recommended. Lowering LDL-C is important to decrease short- and long-term risk of all levels, and therapeutic lifestyle changes are always recommended as a central component of prevention.

The ATP III Guidelines are based in part on studies that have shown that individuals at moderate risk benefit from the addition of statin therapy to therapeutic lifestyle changes. The studies cited include the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) of 6,605 study participants who had a mean baseline LDL-C level of 150 mg/dL [2]. After a 5 year treatment period patients who received lovastatin 20mg or 40 mg had a 37% decrease in major coronary events and a 33% decrease in coronary revascularization procedures compared to patients who received placebo. As shown in Table D-1, The ATP III Guidelines recommend LDL-C lowering drugs for persons with a 10 year risk of 10% or greater. This cut-off was determined after assessing the cost-effectiveness of treatment given the price of lipid lowering medications at the time the guidelines were drafted (approximately $3.00 per day), and acknowledges that on an overall basis, the risk-benefit was favorable at lower individual absolute risk.

Table D-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 [35]

Thus, the benefit of statin therapy (with therapeutic lifestyle changes) for individuals without CHD or CHD risk equivalents who have a moderately high 10 year risk of CHD (10-20%) is well established and endorsed by the ATP III Guidelines. It is notable that the benefit of statin therapy has also been demonstrated for individuals at lower risk. In AFCAPS/TexCAPS 35% of subjects had a 10 year risk less than 10%. Nevertheless, over the 5 year study period 21% of the cardiac events still occurred in these individuals [4]. In this sub-group, treatment with lovastatin reduced the relative risk of a cardiac event by 34% (95% confidence interval -9% to 60%, p=0.10). This did not reach statistical significance, likely due to sample size limitations, but the estimated effect size is consistent with that seen in the overall study population. Benefit of statin treatment in lower risk populations is consistent with the concept that relative risk reduction with statin therapy is largely independent of the pre-treatment absolute risk.

With regards to life-time prevention, the ATP III Guidelines acknowledge that the 10-year risk estimates are less reliable for selecting candidates for medical therapy. The lifetime risk of CHD continues to be significant in the United States with a 1 in 2 risk for

men and a 1 in 3 risk for women who are free of CHD at age 40 years. Consequently, the ATP III Guidelines support the treatment of younger individuals with LDL-C levels of 160-189 mg/dL even when the 10 year risk is less than 10%.

In summary, the importance of primary prevention of CHD is well-established. The value of statin therapy particularly for individuals with a 10-20% CHD risk is accepted. In addition, the benefit of statin therapy in lower risk individuals has also been demonstrated and acknowledged. Thus, as agreed in 2005, the proposed label criteria target a population which merits treatment and can obtain the benefit of CHD risk reduction.

2.2 Treatment Gap

A significant number of persons in the United States are unaware that they have elevated cholesterol. Furthermore, many persons who do know that they have a cholesterol problem are untreated. Finally, among those who are being treated, a significant proportion is not achieving target cholesterol levels. The scope of these problems is demonstrated by two epidemiologic studies summarized below.

- The 1999 to 2000 National Health and Nutrition Examination Survey (NHANES) evaluated men and women aged ≥20 years who were a representative sample of the non-institutionalized civilian US population [5]. Survey participants with hypercholesterolemia were identified (total cholesterol concentration ≥200 mg/dL or use of a cholesterol lowering medication). There were a total of 4,148 such participants of whom 35% were aware of this condition. The proportion of hypercholesterolemic participants who were being treated (with medications) was 12.0%, and the proportion whose hypercholesterolemia was controlled (total cholesterol <200 mg/dL) was only 5.4% (7.5% of men and 3.7% of women).
- The Minnesota Heart Survey is an ongoing population-based surveillance of trends in cardiovascular disease risk factors, morbidity, and mortality. It consists of independent, cross-sectional samples of adults (aged 25-74 years for the 1980 to 1982 survey, and aged 25-84 for subsequent surveys) from the Minneapolis-St Paul, Minnesota metropolitan area [6]. Hypercholesterolemia was defined as a total cholesterol concentration ≥200 mg/dL or use of a cholesterol lowering medication. Results from the 2000 to 2002 survey (of 1,352 participants) found that the age-adjusted prevalence of hypercholesterolemia was 54.9% for men and 46.5% for women. Only approximately 46% of hypercholesterolemic participants were aware of their condition. Only 19% of men and 12% of women were aware of and treating their hypercholesterolemia (with medications) and even smaller proportions were treating it successfully (defined as a total cholesterol concentration <200 mg/dL): 13.1 % of men and 6.0% of women.

Both studies identified very significant awareness gaps of over 50%. Among those who were aware of their hypercholesterolemia there were even larger treatment gaps: about two-thirds of those in NHANES and about 60% of men and 75% of women in the Minnesota Health Survey who were aware of their hypercholesterolemia were not being treated with medications. Of those being treated, significant proportions were achieving

only partial success. It is interesting to note that in both of these studies only half as many women as men were being treated successfully. One explanation for this may be that, at least in primary care settings, women are still less likely than men to be assessed for hypercholesterolemia [36].

Both of the above studies evaluated total cholesterol levels rather than LDL-C levels which are the focus of the NCEP ATP III Guidelines. The Multi-Ethnic Study of Atherosclerosis (MESA) did evaluate LDL-C levels and an analysis assessed the treatment and control of patients in the various ATP III risk categories [37]. MESA is a multicenter cohort study of 6,814 persons aged 45-84 years who were free of clinical cardiovascular disease at study baseline (2000-2002). The 10-year risk of coronary heart disease was calculated with the use of the Framingham Risk Score. Persons who were not taking lipid lowering medications were classified as having dyslipidemia if their LDL-C concentration exceeded their risk group-specific threshold as recommended by ATP III for consideration of drug therapy. All persons treated with lipid lowering medications were classified as having dyslipidemia. The overall prevalence of dyslipidemia was 29.3%. Fifty-four percent of dyslipidemic patients were being treated (with medications) with 75.3% of these treated persons achieving control.

These results appear to be more encouraging than those seen in the NHANES or Minnesota Heart Study with over half of dyslipidemic patients being treated and three-quarters of those achieving control. However, overall only 40% of dyslipidemic patients were successfully treated. It is also instructive to look at the results by ATP III risk categories. When classified in this way, 34.8% of MESA participants were low risk, 43.6% were intermediate risk and 21.6% were high risk. The prevalence of dyslipidemia was 11.7%, 33.6%, and 48.9% across these categories. More than 80% of the low-risk group was treated and nearly all of them were controlled. However, only half of the intermediate and high risk groups were treated and control was achieved in approximately 80% of the intermediate and half of the high risk groups. Thus, whether the MESA data are examined by ATP III risk category or by overall prevalence of elevated LDL-C levels it is clear that there is still a significant treatment gap, particularly for the intermediate and high risk patients.

2.3 Narrowing the Treatment Gap with MEVACOR™ Daily

2.3.1 Responsible promotion of MEVACOR™ Daily is anticipated to increase consumer awareness and treatment of elevated cholesterol

The goal of the promotion campaign for MEVACOR™ Daily will be consumer education and encouragement of greater participation in their health care. Thus, the campaign will emphasize the benefits of lowering cholesterol, the importance of knowing one's cholesterol values, and the appropriate criteria for self-selection and de-selection for MEVACOR™ Daily, emphasizing that the product is not right for everyone. Similar consumer education and participation campaigns in other areas of public health risk, such as smoking, hypertension, and breast cancer screening have resulted in improvements in consumer behavior (see Appendix 7). In the nonprescription environment similar beneficial results have been achieved with smoking cessation, low dose aspirin and, most recently, obesity. Evidence as to whether it would help narrow the

treatment gap can be inferred by the effect of direct-to-consumer (DTC) advertising campaigns of prescription statins. A study evaluated the relationship between heavy television promotion of atorvastatin, pravastatin, and simvastatin, and the frequency of LDL-C goal achievement 6 months later at geographically dispersed primary care practices in the United States [9]. The study found that, overall, high levels of DTC advertising increased the likelihood that patients attained LDL-C goals by 6% ($p<0.001$), although the effect was greatest in patients with the least restrictive ATP III treatment goals (≤160 mg/dL). The MEVACOR™ Daily in-package materials, and internet- and telephone-based assistance programs will further enhance awareness and education among interested consumers beyond that achieved in the broader community by advertising alone. A further advantage will occur through greater ease of access since physician and pharmacist interaction will not be required with the same rigor as for prescription statins.

2.3.2 Adherence to Therapy in the OTC Setting

The concern has been raised that persistence and compliance with OTC statins would be poor [10; 11]. Results from CUSTOM show otherwise. In that study, persistence with therapy (defined as percent of users who completed at least 24 weeks of treatment) was 61%. This is similar to the 56% mean persistence seen after 6 months of prescription statin therapy in a retrospective cohort database study [12]. Furthermore, in CUSTOM, appropriate discontinuation of therapy was encouraged (e.g., if LDL-C goal was not reached or if unexplained muscle pain developed), and these appropriate discontinuations were not excluded when the persistence figure noted above was calculated. If the participants who discontinued appropriately are combined with the 61% who persisted with therapy, a total of 79% of users made an appropriate persistence decision. Thus, the persistence with lovastatin OTC was consistent with, if not better than, that seen for prescription statins. Further evidence of good compliance with MEVACOR™ Daily can be obtained from the magnitude of the LDL-C lowering in CUSTOM. Among participants with LDL-C values at baseline and at study end (week 26) the mean reduction in LDL-C was 25.2% for participants with fasting levels and 20.6% when participants with non-fasting levels were included. These effects are consistent with the magnitude of effect seen in EXCEL in which lovastatin 20 mg q.h.s. decreased LDL-C by a mean of 24% [1].

Persistence and compliance with OTC statins beyond 6 months was evaluated in a 6 month Actual Use study of lovastatin OTC 10 mg which had 2 consecutive 6-month extensions for a total of 18 months of therapy. Persistence was measured by the number (%) of patients who returned for the next visit and who had taken at least one tablet of lovastatin 10 mg since their previous visit. At the end of the first 6-month period, persistence was 69.8%; at the end of the second 6-month period (i.e. after 12 months) it was 56.2%; and at the end of the study (i.e., after 18 months) it was 44.6%. This degree of persistence was comparable to the 50% mean persistence after 12 months of prescription statin therapy reported in the database study referenced above [12]. Importantly, these numbers reflect study participant-initiated use of MEVACOR OTC drug, and they are relevant to consumer behavior in the unsupervised environment.

Compliance with therapy in the 18 month lovastatin OTC study was measured as the number of tablets consumed divided by the number of days that the patient had study medication in a specified time period. Patients were considered compliant if they took at least 75% of their tablets, as determined by a tablet count at the time of the return study visit. Study visits occurred at 3 month intervals and, during the two 6-month extensions, between 84.5% and 92.5% of the patients remaining on therapy took at least 75% of their medication in the given interval. Thus, compliance was very good indicating that those who remained on treatment tended to be very compliant. The compliance data were supported by the LDL-C reductions which were consistent with the LDL-C reductions seen in randomized, placebo-controlled clinical trials of lovastatin 10 mg.

2.3.3 Consumers' diet and level of exercise will be maintained or improved with the availability of an OTC statin

Exercise and an appropriate diet are cornerstones of lipid management. They should always be recommended and, with the exception of higher risk patients, are initiated prior to consideration of cholesterol lowering medications. Even when medications are indicated, proper diet and exercise are expected to continue.

Concern has been expressed that the availability of OTC statins might lead individuals to disregard these lifestyle habits [13; 14]. In fact, there is evidence to suggest that the opposite would happen. First, the practices of prescription treated and untreated moderate risk consumers were queried and compared in a large survey [8]. Overall, more treated consumers than untreated consumers followed health conscious habits such as not smoking, trying to lose weight, and eating a low-fat diet. There were two areas, however, where the two groups of consumers were similar: eating heart-healthy foods, and exercising. Less than a third of consumers in either group reported regular exercise, highlighting the real world difficulty that people have with complying with that directive. Treated consumers were also significantly more likely to know their exact total cholesterol than untreated consumers (42% vs. 26%) suggesting that the treated consumers were generally more engaged in the maintenance of their health.

Results from surveys of consumers interested in using an OTC statin have shown that these are persons who describe themselves as being informed on health prevention issues and are already engaged in appropriate lifestyle activities. A large majority reported getting health information from health care providers (72%) or from the internet (65% to 74%). Forty-four percent reported exercising or maintaining a healthy weight and 42% to 45% reported watching their diet or choosing low fat options. Thus, the evidence supports that these are informed individuals who are currently actively engaged in maintaining their health. Would these people abandon their lifestyle efforts with the appearance of an OTC statin? Results from CUSTOM indicate otherwise. Self-reported dietary habits were maintained or improved in 98% of users of lovastatin OTC. The participants also completed a dietary assessment questionnaire and by the end of the study, 27% of them had improved their diets. Self-reported exercise habits were maintained or improved in 94% of the participants. Thus, the evidence supports that the

availability of an OTC statin will reinforce the importance of lifestyle management to the consumers who are interested in this treatment option.

2.3.4 Published estimate of the impact of an OTC Statin on CHD prevention in the U.S. population

A newly published (Oct-2007) study used population impact measures to estimate the impact on CHD events if MEVACOR™ Daily was available (see Appendix 10). Data from the National Health and Nutrition Examination Survey III were used to provide the numbers of Americans at risk of CHD in each of three different risk categories. These categories were based on the ATP III risk score and were low (<10% risk), moderate (10-20% risk) and high (>20% risk). The 37% decrease in risk of a first major coronary event that was seen in AFCAPS was used as the effectiveness of nonprescription lovastatin for the low to moderate groups. This was compared to a 16% risk reduction due to therapeutic lifestyle changes for the low to moderate risk groups. The high risk group was assessed for a 36% risk reduction with use of prescription statins. The numbers of CHD events prevented was estimated for a 5 year period and are summarized in Table D-2 below:

Table D-2
Number of CHD Events Prevented in the U.S. over a 5-Year Period by OTC Statins and Lifestyle Changes

10-year baseline risk (%)	Intervention	Proportion of US population at risk	Proportion who would initiate intervention	Proportion who would persist with intervention	Relative Risk Reduction	Number of CHD events prevented
5	MEVACOR™ Daily	0.817	0.20	0.56	0.37	326,227
5	Lifestyle	0.817	0.52	0.65	0.16	425,733
15	MEVACOR™ Daily	0.155	0.20	0.56	0.37	185,674
15	Lifestyle	0.155	0.52	0.65	0.16	242,308
25	Prescription Statins	0.029	0.80	0.59	0.36	237,406

Therapeutic lifestyle changes prevented more CHD events than MEVACOR™ Daily due to greater proportions of the population initiating and persisting with lifestyle changes than with MEVACOR™ Daily. Nonetheless, the analysis demonstrated that the availability of MEVACOR™ Daily would prevent over 500,000 CHD events in the low and moderate risk populations over a 5 year period.

Dr. Eric Brass et al. (see Appendix 9) performed an analysis using the CUSTOM data, applying more conservative assumptions, and reached a similar qualitative conclusion regarding the public health benefit of nonprescription lovastatin.

2.4 Benefit Summary

It has been estimated that there are 23 million Americans without CHD or CHD equivalents who have a 10-year Framingham Risk Score of 10-20% [15]. Based on the results of NHANES, the Minnesota Heart Survey, and MESA, half or more of these people are untreated. Surveys have found that there is interest among patients and support among physicians and pharmacists for an OTC statin. There is evidence that persistence and compliance with an OTC statin would be similar to that for prescription statins and that consumers' diet and exercise patterns would be maintained or improved. Thus, the availability of an OTC statin clearly has the potential to help narrow the treatment gap. In fact, a study using population impact measures determined that the availability of MEVACOR™ Daily would prevent over 500,000 CHD events in a 5-year period.

3. Risks

The remaining concerns outlined by FDA following the 2005 Advisory Committee hearing included a number of potential risks secondary to inappropriate use by consumers. These were:

- use by women younger than 55 years of age;
- use by persons with lower risk of CHD;
- inappropriate use in the presence of muscle symptoms and with interacting medications;
- use by persons with undiagnosed chronic liver disease; and
- use by women of childbearing potential.

These concerns are addressed in detail below. The concern regarding use by women younger than 55 years of age is based on two issues: a relatively low risk of CHD, and the possibility of use while still of childbearing potential. This concern will therefore be addressed under those two categories.

3.1 Use by persons with relatively low risk of CHD

Persons who have a low Framingham Risk Score can still be at risk of a cardiac event in the short-term. Post-hoc analyses of the data from AFCAPS/TexCAPS evaluated how the NCEP ATP III guidelines would have affected this study cohort [4]. Of the 6,605 study participants, 65% would have met the ATP III criteria for treatment with a lipid lowering medication. Over the 5 year study period, 79% of the cardiac events occurred in this sub-group of patients. The remaining 35% of the population had a mean 10 year CHD risk of 6.4%, as determined by the event rate in the placebo group. Interestingly, lovastatin therapy resulted in very similar reductions in the relative risk of a cardiac event in both sub-groups (39% for the higher risk group and 34% for the lower risk group).

Evidence is accumulating that the Framingham Risk Score may not accurately predict risk of cardiovascular disease in all patients, including in those with two or more known major risk factors. This appears to be particularly true for women for whom, even up to the age of 80 years, more than three-quarters have a 10-year Framingham Risk Score below 10% [16]. This despite the fact that cardiovascular disease is the leading cause of

death among women in the United States [17] and is responsible for more deaths in women than all forms of cancer combined [18]. In fact, the lifetime risk of CHD after age 40 years has been estimated at 32% for women (and 49% for men) [16]. The studies summarized below demonstrate how even persons with low Framingham Risk Scores can be at significant risk for CHD.

A retrospective study evaluated men aged ≤55 years and women aged ≤65 years who were admitted with a myocardial infarction to the Coronary Care Unit of a Wisconsin medical center between 01-Jan-1998 and 31-Dec-2000 [38]. Patients with a history of CHD or CHD equivalent were excluded. The goal of the study was to determine each person's level of risk and whether or not they would have met the criteria for medical management if they had presented to their physicians before the myocardial infarct. Overall, only 25% of the 222 patients would have qualified for medical therapy if they had presented prior to their event although their subsequent infarct proved they were high risk patients. When evaluated by gender, 59% of men and 82% of women did not qualify for pharmacotherapy based on current criteria. The mean age of the patients was 50 years and 25% were women. LDL cholesterol was ≥130 mg/dL in 42% of the group; only 16% of the group had LDL cholesterol ≥160 mg/dL. NCEP ATP III Guidelines were used to calculate the 10-year risk for coronary events for the 222 study patients. Multiple major risk factors (age, smoking, hypertension, HDL <40 mg/dL, family history of CHD) were present in 49% of patients. The 10 year calculated CHD risk was stratified according to the number of major risk factors and the LDL cholesterol level. The majority of patients who had just had a myocardial infarct had either 0-1 risk factors (50%) or a 10 year CHD risk<10% in the presence of 2 or more risk factors (20%). All women had at least one risk factor and the mean number of major risk factors was higher in women than in men (2.9 vs. 1.5 risk factors, $p<0.001$). Nonetheless, 95% of the women had a calculated 10 year CHD risk of less than 10% and the remaining 5% had a calculated 10 year CHD risk of 10-20%. These low risk scores in the face of CHD may be at least partly explained by risk factors that are not included in the Framingham Risk Score calculation such as physical inactivity or weight. For example, 82% of the population in the above study were overweight (37%), obese (28%), or grossly obese (17%).

Another line of evidence that persons with low Framingham Risk Scores can still be at significant risk for CHD comes from studies of coronary artery calcification (CAC). CAC as assessed by electron beam tomography has been demonstrated to be directly related to the extent of atherosclerotic disease [25] and to future cardiac events [27]. Studies have demonstrated that a significant percentage of people with low Risk Scores can have CAC scores consistent with significant atherosclerosis (defined as a score ≥75, i.e. at or above the 75th percentile for age and sex).

- In one cross-sectional study of 5,931 men and 2,618 women (mean ages 53 and 51 years, respectively) CAC scores ≥75 were present in 20% of low-risk persons [24]. Women were much more highly represented than men in the low risk group (84% vs. 48%) but advanced CAC was present in 19% of these low-risk women (and in 21% of low risk men). There was an incremental increase in the prevalence of advanced

CAC with an increasing number of the following risk factors: obesity, family history of premature CHD (before age 55 years), and physical inactivity.

- In another study, 102 asymptomatic women (mean age 51 years) who were sisters of persons with documented premature CHD had a mean Framingham Risk Score of only 2% [27]. However, 32% of these women had a CAC score greater than 75. By design, all of these women had a family history of premature CHD and 46% of them were obese as well.

Thus, individuals with low Framingham Risk Scores may still be at significant risk for CHD. Family history of premature CHD, obesity and physical inactivity, all factors not captured in the Risk Score, appear to be important determinants of increased CHD risk.

The Framingham Risk Score estimates the 10 year risk of developing cardiovascular disease (CVD) but many people have a much longer life expectancy than 10 years. A study estimated the lifetime risk of developing CVD using the data from all Framingham Heart Study participants who were free of CVD at 50 years of age [17]. There were 3,564 men and 4,362 women who were followed through 2002 until the occurrence of a first CVD event, death, attainment of 95 years of age, or date of last follow-up. With this longer time frame it became evident that many persons with low 10 year risks had remarkably high lifetime risks. The study estimated that more than half of men and nearly 40% of women free of CVD at age 50 years will develop CVD during their remaining lifespan. For example, a 50 year old nonsmoking, non-diabetic man with total cholesterol of 250 mg/dL, HDL of 60 mg/dL, and an untreated systolic blood pressure of 160 mmHg (i.e. 2 major risk factors: age and hypertension) had an estimated 10 year risk of 7% but an average lifetime risk of CVD of nearly 70%. A 50 year old woman with the identical risk factors had an estimated 10-year risk of only 2% but a lifetime risk of 50%.

The above studies demonstrated that a low Framingham Risk Score guarantees neither the absence of atherosclerotic cardiac disease (as measured by CAC) nor the absence of a cardiac event in the short- or long-term future. The above studies also demonstrated that the Framingham Risk Score particularly underestimates disease risk in women. In an effort to improve risk estimation and subsequent treatment of women, an expert panel has developed the Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women.

The most recent update (published in March 2007) to the AHA Guideline, "Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women" acknowledges that women with one or more risk factors may have a broad range of CVD risk [23]. The update advocates placing greater emphasis on lifetime risk as opposed to the short-term absolute risk defined by the Framingham Risk Score. It furthermore proposes a classification into three categories of CVD risk in women as shown in Table D-3 below.

Table D-3
Classification of CVD Risk in Women, 2007 Update to the AHA Guideline

Risk Status	Criteria
High Risk	Established coronary heart disease
	Cerebrovascular disease
	Peripheral arterial disease
	Abdominal aortic aneurysm
	End-stage or chronic renal disease
	Diabetes mellitus
	10-year Framingham global risk >20%
At Risk	**1+ major risk factors for CVD, including:**
	Cigarette smoking
	Poor diet
	Physical inactivity
	Obesity, especially central adiposity
	Family history of premature CVD (<55 years of age in men, <65 years of age in women)
	Hypertension
	Dyslipidemia
	Evidence of subclinical vascular disease (e.g. coronary calcification)
	Metabolic syndrome
	Poor exercise capacity on treadmill and/or abnormal heart rate recovery after stopping exercise
Optimal Risk	Framingham global risk <10% and a healthy lifestyle with no risk factors

[23]

The guidelines recommend pharmacotherapy for all women defined as 'high risk' in this classification and for 'at risk' women with multiple risk factors and a Framingham Risk Score of 10 to 20%. Pharmacotherapy is also recommended for 'at risk' women if they have an LDL-C ≥ 160 mg/dL and multiple risk factors even if their Framingham Risk Score is less than 10%.

In summary, persons with low Framingham Risk Scores, especially women, can still be at significant risk of a cardiac event and could benefit from lipid lowering therapy. A post-hoc analysis of AFCAPS/TexCAPS data showed that treatment of the lower risk study patients with lovastatin decreased the relative risk of a cardiac event by 34%.

3.2 Inappropriate use in the presence of muscle symptoms and with interacting medications

Overall Muscle Safety

The risk of myopathy with all statins is dose-dependent and has been shown to be very low with lovastatin 20 or 40 mg. EXCEL was a study of 8,245 patients who were randomized to placebo or lovastatin at a dosage of 20 mg once daily, 40 mg once daily, 20 mg twice daily, or 40 mg twice daily for 48 weeks [1]. No patients experienced rhabdomyolysis and myopathy was experienced by 5 patients: 1 patient who received 40 mg once daily and 4 patients who received 40 mg twice daily. In AFCAPS/ TexCAPS there were no cases of myopathy and 3 cases of rhabdomyolysis during the 5 year treatment period: 2 in patients who received placebo, and 1 (after surgery for prostate

cancer) in a patient who received lovastatin [2]. The FDA postmarketing database was examined (through 31-July-2001) by FDA to determine reporting rates for rhabdomyolysis with statin monotherapy and with statin/ gemfibrozil therapy [39]. Rhabdomyolysis was defined as CK>10,000 IU/L, signs and symptoms (myalgia, myopathy, gait disturbance) and a clinical diagnosis of rhabdomyolysis. The reporting rates for all statins, except for cerivastatin, were similar and for lovastatin they were: 0.12 reports for 100,000 prescriptions of monotherapy, and 2.84 reports for 100,000 prescriptions of lovastatin/ gemfibrozil therapy.

The issue of muscle symptoms with the use of MEVACOR™ Daily also encompasses concomitant use of prescription medications because of potential drug interactions that can increase the risk of myopathy. Lovastatin is a substrate for cytochrome P450 isoform 3A4 (CYP3A4) but is not an inducer or inhibitor of CYP3A4 or of any other cytochrome P450 isoform. Thus, lovastatin does not affect plasma concentrations of other drugs metabolized by any of the cytochrome P450 isoforms. However, because lovastatin is metabolized by CYP3A4, medications which are potent inhibitors of CYP3A4 can reduce its elimination, thereby increasing plasma levels of lovastatin and increasing the risk of myopathy. The risk of myopathy is also increased with concomitant use of other lipid-lowering medications (fibrates, especially gemfibrozil and niacin) that are not potent CYP3A4 inhibitors but which can cause myopathy when given alone.

At the time that AFCAPS/TexCAPS was conducted the effect of concomitant medications was not well understood. Therefore, patients were allowed to receive potent CYP3A4 inhibitors in addition to lovastatin. Table D-4 lists muscle adverse experiences of interest that were serious, drug-related, or caused discontinuation that occurred while patients were taking one or more potent CYP3A4 inhibitor(s). The data demonstrate that even with this concomitant therapy the occurrence of muscular adverse events with lovastatin 20 to 40 mg was still very low and very similar to that for placebo. There were no reports of myopathy or rhabdomyolysis in these patients taking concomitant CYP3A4 inhibitors. These observations support the substantial safety margin associated with lovastatin 20 mg.

Table D-4
Muscle Adverse Experiences with Concomitant CYP3A4 Inhibitor -
AFCAPS/ TexCAPS

	Lovastatin 20 to 40 mg (N=535[†])		**Placebo (N=512[‡])**	
Adverse Experience	**N**	**%**	**N**	**%**
Any musculoskeletal adverse experience	42	8	39	8
Myalgia	3	1	4	1
Muscle weakness	1	0.2	2	0.4
Myopathy/ Rhabdomyolysis	0	0	0	0
[†]Erythromycin (379), clarithromycin (107), ketoconazole (42), itraconazole (51), nefazodone (4) [‡]Erythromycin (370), clarithromycin (110), ketoconzaole (21), itraconazole (42), nefazodone (5)				

[2]

Improvements to OTC Labeling

In response to the 2005 NDA Action Letter, Merck significantly revised the material regarding muscle symptoms contained in the package for MEVACOR™ Daily. The revisions that were made were:

- Expanded warning language that includes explanatory text and the potential consequences of not heeding the warning.
- Inclusion in the package of a 3" by 5" refrigerator reminder magnet displaying the muscle and the prescription medication (potential drug interaction) warnings.
- Identical warning language regarding muscle symptoms in all three of the internal package materials: the Quick Start Guide, the Patient Package Insert, and the Magnet
- Highlighting in red type of the entire muscle warning text (found in two different locations) in the Patient Package Insert
- Added language to the prescription medication warning that links it to the muscle warning.

Successive stages of consumer testing were conducted to evaluate these revisions. These stages culminated in the conduct of the Muscle Warning Comprehension Study #088 which evaluated the final proposed materials in 366 respondents including an augmented set of low literacy respondents. The study demonstrated that the currently proposed package materials effectively communicated information about unexplained muscle symptoms. Specifically, 98% of the respondents understood that if such symptoms are experienced, MEVACOR™ Daily should be discontinued. Additionally, 94% of the respondents knew that these symptoms could occur any time while using MEVACOR™ Daily, and 82% knew that ignoring these symptoms could have serious consequences. Thus, the results of the Muscle Warning Comprehension Study indicate excellent comprehension. Higher compliance than that seen in CUSTOM with the muscle pain warning can be anticipated.

The Pivotal Label Comprehension Study #087 assessed consumer comprehension of the package label for MEVACOR™ Daily, including comprehension of its warnings and cautions. Study respondents were asked about use with a number of concomitant medications (oral antibiotics, oral antifungals, cholesterol medications, and large quantities of grapefruit juice). The study respondents showed excellent comprehension with 91-95% of the non-low literacy sample providing correct or acceptable answers regarding use of these medications. The low literacy sample scored somewhat lower (79-92% correct or acceptable answers) but still showed good comprehension. These results further demonstrate that appropriate use of MEVACOR™ Daily can be anticipated with regards to the issue of muscle symptoms.

In conclusion, large long-term placebo-controlled clinical trials have demonstrated that myopathy with lovastatin 20 mg occurred rarely and its frequency was not increased with use of potent CYP3A4 inhibitors. The label comprehension studies that are included in this application demonstrated that consumers clearly understood what actions to take if they developed symptoms consistent with myopathy. Furthermore, they clearly

understood what actions to take in the event of concomitant use of medications which would increase the risk of myopathy.

3.3 Use by persons with undiagnosed liver disease

Although the 2005 Advisory Committee voted unanimously that liver function testing is not required for MEVACOR™ Daily, the FDA subsequently requested "sufficient evidence that the risk of hepatotoxicity is minimal in patients with common asymptomatic liver disease" or "sufficient evidence that consumers can make clinical safety assessments of hepatic risk before initiating therapy." Results from three studies not previously available are summarized below to support the conclusion that there is very low risk of hepatotoxicity in patients with asymptomatic liver disease.

A retrospective cohort database study sponsored by Merck was conducted to evaluate patients with pre-existing liver disease who were treated with lovastatin. Patients were eligible if they had pre-existing elevated serum transaminase levels or a diagnosis of a liver disease (including chronic viral hepatitis B or C without liver failure, other chronic hepatitis, alcoholic liver disease, and metabolic diseases such as hemachromatosis). There were 93,106 patients who were eligible for this study and 14.5% of them had received at least one lovastatin prescription. The median length of lovastatin exposure was 9 months. The primary outcome variable was Hy's Law (a pattern of liver test abnormalities associated with a poor prognosis among patients with drug-induced liver disease). The secondary outcomes were the development of liver injury or cirrhosis/ liver failure. There was no evidence that lovastatin use was associated with adverse hepatic outcomes. In fact, lovastatin use was associated with substantial and statistically significant decreases in all of these outcomes (incidence rate ratio for Hy's Law: 0.28 [95% CI 0.12-0.55], and for combined secondary outcomes: 0.48 [95% CI 0.42-0.55]). Furthermore, there was evidence of a dose response with a clear association between higher lovastatin dose and fewer outcome events for combined secondary outcomes (test for trend; $p<0.0001$). There were too few cases of Hy's Law to assess for a dose response.

Another retrospective database study evaluated the use of lovastatin by patients with elevated baseline liver enzymes [19]. There were 3 cohorts of patients: cohort 1 had elevated enzymes and received lovastatin; cohort 2 did not have elevated enzymes and received lovastatin; and cohort 3 had elevated enzymes and did not receive lovastatin. The mean duration and dose of lovastatin was very similar between cohorts 1 and 2 (396 vs. 472 days; and 23 vs. 24 mg/day). After 12 months of follow-up, patients in cohort 1 had comparable mild-moderate enzyme elevations vs. patients in cohort 3 (6.6% vs. 11%, $p=0.2$)) but significantly fewer severe elevations (0% vs. 5.5%, $p<0.01$). Patients in cohort 1 had a higher incidence of mild-moderate enzyme elevations vs. patients in cohort 2 (6.6% vs. 3% $p=0.03$) but not of severe elevations (0% vs. 0.3%, $p=0.9$). No one in cohorts 1 or 2 developed a case meeting Hy's Law whereas 3.5% of patients in cohort 3 did ($p<0.01$ vs. cohort 2, and $p=0.03$ vs. cohort 1). These results showed that patients with elevated baseline liver enzymes were not at a higher risk of hepatotoxicity from lovastatin than patients with normal enzymes.

Finally, a third publication evaluated statin use in subjects with hepatic steatosis (non-alcoholic fatty liver disease) who were enrolled in the Dallas Heart Study [20]. There were 2,287 Dallas Heart Study patients in whom hepatic triglyceride content was measured and 6% (140 patients) of them were taking statin monotherapy. Study results showed that statin use was not associated with a greater prevalence of hepatic steatosis or elevated serum alanine transaminase (ALT), or with an increased prevalence of elevated ALT levels in subjects with hepatic steatosis.

In summary, these large studies clearly demonstrated that the risk of hepatotoxicity with lovastatin use is minimal in patients with pre-existing liver disease. This information reassures that consumers who have undiagnosed asymptomatic liver disease will be at low risk for adverse hepatic events due to use of MEVACOR™ Daily. For those consumers with diagnosed liver disease, the proposed Drug Facts for MEVACOR™ Daily includes a warning to 'ask a doctor before use if you…have liver disease'.

3.4 Use by pregnant or nursing women, or women of childbearing potential

Following the 2005 Advisory Committee hearing, the FDA acknowledged any fetal risk from lovastatin is possibly theoretical and probably small, and required that a revised nonprescription label be developed and tested in comprehension and self-selection studies to further minimize any potential risk. In response, Merck has revised the Drug Facts portion of the carton label by expanding the pregnancy-related language to include women of childbearing potential. The potential consequences of lovastatin use during pregnancy have also been added. Thus, the pregnancy related language has been expanded from "Do NOT use if you are pregnant or breast-feeding" to "If pregnant or breast-feeding, or think you may become pregnant, do not use. This product may cause problems in the unborn child". Potential use by pregnant or nursing women or women of child-bearing potential was evaluated in the SELECT Study.

3.4.1 Pregnant or Nursing Women

The current information on pregnancy outcomes following exposure to lovastatin or to simvastatin, which is structurally very similar to lovastatin was reviewed. Information was collected from 3 sources: Merck's Worldwide Adverse Experience System database; the Swedish Medical Birth registry which contains prospectively collected information on nearly all pregnancies resulting in deliveries in Sweden since July 1995; and from the published clinical literature. The largest publication was a case series of 477 reports with exposure to lovastatin or simvastatin [3]. The authors concluded that there was no pattern of congenital anomalies and no indication of association between maternal exposure to either statin and adverse pregnancy outcomes. Review across the 3 sources of information listed above did not identify any pattern of findings. Importantly, all 3 sources included prospectively collected information. Prospective reports are less likely to be influenced by reporting bias and are more likely to reflect pregnancy outcomes in the exposed population as a whole. The Teratogen Information System (TERIS) summary for lovastatin was also obtained. The summary, which was written by a team of clinical teratology experts after completing a thorough literature review, concluded that the risk of teratogenic effect was "Unlikely". Thus, the information continues to support

the assessment made by the FDA in 2005 that the risk of toxicity to the fetus is probably small and may be theoretical.

Any risk to the fetus is further minimized by the effective label warning against use by pregnant women. The revised pregnancy related language in Drug Facts for MEVACOR™ Daily was evaluated in SELECT. In SELECT four pregnant women, one nursing woman, and 21 women who said that they may become pregnant evaluated the package for MEVACOR™ Daily. All 26 women made the appropriate decision to not purchase the product. These results are consistent with those seen in the CUSTOM study in which all 12 pregnant women who evaluated lovastatin OTC decided not to purchase.

3.4.2 Women of Childbearing Potential

Women of child-bearing potential can be defined as women who have not yet reached menopause. The age of natural menopause in the United States was recently evaluated in the multiracial/ multiethnic Study of Women's Health Across the Nation (SWAN) [21]. A total of 16,065 women participated in the cross-sectional survey and 3,150 of them participated in the cohort study. Natural menopause was defined according the World Health Organization as at least 12 consecutive months of amenorrhea not due to surgery or other obvious cause. The overall adjusted median age at natural menopause was 51.4 years. These results are nearly identical to those of the New York University Women's Health Study of 14,275 women (predominantly white women from New York City), using a 6-month absence of menstrual period definition [22]. In this study, the median age of menopause was 51.3 years. The probability of being menopausal increased rapidly thereafter and was greater than 80% by age 55 years. Clearly, the age limit specified by the Drug Facts for MEVACOR™ Daily (≥55 years for women) discourages use by the vast majority of premenopausal women.

In SELECT, a small percentage of women younger than 54 years of age chose to purchase MEVACOR™ Daily (13%, 48/378). As per the Data Summarization Plan, if a woman had passed her 54th birthday, she was considered to be within the label criteria. The distribution of positive purchase decisions by women aged <54 years are displayed in Table D-5 below.

Table D-5
Distribution of Women Less than 54 Years Old in SELECT

Age (years)	No. who evaluated and provided purchase decision (N=387)	No. (%) who chose to purchase (N=48)
<40	119	6 (5)
40-44	55	4 (7)
45-49	102	17 (17)
50-53	111	21 (19)

Of the women younger than 54 years who chose to purchase, 21/48 or 44% were 50 to 53 years old. SELECT did not systematically collect information on whether a woman had reached menopause but, based on the study results summarized above, approximately half of the women aged 50-53 years could be considered menopausal.

Fertility declines prior to menopause. The Centers for Disease Control and Prevention summary of births for 2004 reported an overall birth rate of 8.9 per 1000 women aged 40 to 44 years, and an overall birth rate of 0.5 per 1000 women aged 45 to 54 years [42]. These statistics included births to women who successfully undertook various fertility treatments. These women are clearly under the care of a physician and actively seeking to become pregnant, and should not be inadvertently taking medications contraindicated in pregnancy. Thus, exposure to MEVACOR™ Daily during pregnancy in women over 45 can be considered to be very unlikely.

A concern may lie in women who inadvertently become pregnant while taking MEVACOR™ Daily and the natural fertility rate in these women would be of interest. Natural fertility rates are difficult to study in contemporary developed countries due to contraceptives, voluntary sterilization, or conversely, fertility treatments. However, studies of relevant populations have been performed and natural fertility declines sharply at age ≥ 40 years with exceedingly low rates between the ages of 45 and 49 years [40; 41].

In summary, the results from SELECT demonstrated that the current labeling was largely effective in limiting use to women in the appropriate age range (55+ years). The vast majority of women in this age range are menopausal. Of the women in SELECT who were younger than 54 years and who chose to purchase the product, 38/48 or 79% were 45 to 53 years of age. This is an age range when natural fertility has decreased to very low levels or when, in many cases, menopause has been reached. Thus, the risk of inadvertent exposure to MEVACOR™ Daily during pregnancy can be expected to be very low. As acknowledged by the FDA and supported by the review of current information, the risk of fetal toxicity is small and may be theoretical. Thus, the proposed labeling for MEVACOR™ Daily adequately minimizes fetal risk. The data clearly establish that the fetal risk from MEVACOR™ Daily is very small, and that the label will result in OTC consumers using MEVACOR™ Daily very rarely while pregnant. Thus, any public health risk is exceedingly low and is offset by the drug's benefits.

3.5 Other Potential Risks

Concerns about potential risks of OTC statins have appeared in the published clinical literature. These include:

- the absence of treatment of other lipid abnormalities such as low HDL cholesterol (HDL-C) [43]; and
- the risk of inappropriate use by high-risk patients [13; 44; 45];
- restrictions to prescription statin use by prescription drug benefit managers and managed care organizations in order to control drug costs [46].

The MEVACOR™ Daily Self-Management System (which is detailed in Section C, MEVACOR™ Daily Self-Management System and Marketing Plans) is designed to support appropriate consumer behavior. This System will help identify persons who are inappropriate for MEVACOR™ Daily, whether due to a less than satisfactory response to the product, other lipid abnormalities, or a higher CHD risk. These individuals will then be directed to seek appropriate professional medical attention. Indeed, a large survey of

consumers, physicians, and pharmacists found that the large majority (83%) of interested consumers would speak with their physicians prior to using an OTC statin [7].

High-risk consumers (those with preexisting cardiovascular condition, diabetes, or a calculated Framingham risk of greater than 25%) should receive aggressive LDL-lowering therapy. MEVACOR™ Daily represents non-optimal therapy for these persons as compared with higher dose statin therapy, but when compared with no therapy would clearly be associated with substantive risk reduction. Thus, the question becomes how these high risk consumers will behave in the setting of OTC lovastatin. Potential positive health benefits include using MEVACOR™ Daily in place of no therapy and being directed to a health care professional for more aggressive therapy based on a review of the Self-Management System or based on an inadequate response to MEVACOR™ Daily. Adverse health impact would result if MEVACOR™ Daily is used as a substitute for more supervised, higher-dose statin therapy. CUSTOM provides data that directly addresses these possibilities.

The cohort of consumers who chose to use MEVACOR™ Daily in CUSTOM had a range of Framingham CHD risk scores and included high risk persons, defined as those with a history of CHD, diabetes or stroke. These high risk users made up a small percentage of the total user group (16%, 167/1061). Nearly three-quarters (74%) of them consulted with their physician either prior to using MEVACOR™ Daily (97/167) or during the course of the study (26/167); this implied that they received their physicians' assent to its use as part of their integrated, supervised care. Of the high risk users who started MEVACOR™ Daily without first consulting their physician, 66% (46/70) of them were not on any prescription lipid-lowering therapy although they clearly should have been as per ATPIII guidelines. While lovastatin 20 mg may not have been the optimal statin dose for these individuals it still was preferable to no therapy at all.

A published analysis of the CUSTOM data by Dr. Eric Brass assessed the potential public health impact MEVACOR™ Daily, including the impact of treating higher risk consumers [28]. In order to do this, Dr. Brass created a hypothetical cohort of 1 million consumers with the same distribution of Framingham risk scores as the CUSTOM participants as this represents a data-based estimate of what the consumer profile will be in the marketplace. Consumers with a history of CHD, diabetes, stroke or with a Framingham Risk Score of greater than 20% were considered to be higher risk. The behavior of this higher risk sub-group in CUSTOM with regards to percentage otherwise untreated vs. percentage who were diverted from optimal prescription medications was modeled as reflective of marketplace behaviors. His analysis determined that on a population basis there continued to a significant benefit in terms of the number of CHD events prevented even with the degree of diversion of high risk consumers estimated in CUSTOM using conservative assumptions. This population wide benefit persisted even if up to 80-90% of the higher risk consumers were diverted from optimal therapy, a percentage that enormously exceeded the diversion that was observed in CUSTOM. Further, this conservative analysis did not include the benefit to previously untreated consumers motivated to obtain optimal therapy after reviewing the MEVACOR™ Daily system without ever using the OTC drug.

In SELECT, among the consumers who wanted to purchase MEVACOR™ Daily, the proportion that was high-risk was also low (16%, 67/419). Similar to the results of CUSTOM, 67% (45/67) of these individuals were not on any lipid-lowering therapy. As per the design of the study, participants were not allowed to consult with their physician prior to making a purchase decision. However, half (11/22) of the high risk individuals who were on therapy stated that they would talk to their physician about this product. Thus, only 16% (11/67) of those at high risk who wanted to purchase would have substituted MEVACOR™ Daily for prescription therapy without discussing this with their physician. Thus, the results of both SELECT and CUSTOM indicate that inappropriate use by high-risk consumers would be limited and would not negate the public health potential of MEVACOR™ Daily availability.

Finally, concern has been expressed that, if an OTC statin were available, managed care organizations would limit access to prescription statins and require use of the OTC statin to control costs. This possibility was evaluated in a study that surveyed 12 managed care organizations (covering approximately 100 million lives), 4 pharmacy benefit managers (covering approximately 200 million lives), and 3 large employers (providing medical benefits to nearly 1.4 million active and retired employees) [47]. The survey results showed that payers recommended following the NCEP ATP III Guidelines and allowed physicians to make prescribing decisions for statins, which the payers viewed as life-saving drugs. None of the organizations interviewed said they would change these policies with the introduction of an OTC statin. Two-thirds of the managed care organizations and 3 of the 4 pharmacy benefit managers anticipated short-term increases in plan costs following such an introduction due to increased awareness of hypercholesterolemia, supporting the postulated secondary public-health benefits associated with an OTC statin. However, these individuals and organizations also felt that there would subsequently be long-term savings due to, not only the availability of a lower-cost OTC option, but also due to improved care of hypercholesterolemic patients. Thus, these results support the conclusion that access to prescription statins would not be affected by the launch of a low-dose OTC statin.

4. Benefit/Risk Conclusion

Following the 2005 Advisory Committee deliberations, the FDA outlined the residual issues which needed resolution prior to approval for OTC MEVACOR™. These centered around the consumers' ability to appropriately self-select for use of the product based on label information. In response, the product labeling and in-package materials were accordingly revised and tested. The final proposed materials were evaluated in representative and low literate populations in two consumer comprehension studies. The Pivotal Label Comprehension Study #087 demonstrated effective communication of the key usage directions, warnings, and cautions on the package label. The Muscle Warning Comprehension Study #088 demonstrated excellent comprehension of warning language regarding unexplained muscle pain, tenderness or weakness.

The self-selection study (SELECT #086) showed meaningful improvement in appropriate self-selection in women <55 years of age and in women of childbearing potential. However, the SELECT results were similar to those of CUSTOM for its third goal of

minimizing purchase by low CHD risk individuals, despite the marked decrease in intent to purchase by women under the age of 55. In both CUSTOM and SELECT, women made up a disproportionate number of these low risk individuals. The target population identified by the MEVACOR™ Daily label was endorsed by the 2005 Advisory Committee, and is consistent with NCEP Guidelines for treatment. The fact that the label allows lower risk women to use the product is a function of the Framingham Risk Score. Even up to the age of 80 years, more than three-quarters of women have a 10-year Framingham Risk Score of less than 10% [16]. Recent AHA Guidelines [23] for preventing CHD in women recognize this and urge treatment for these so-called "lower risk" women. Thus, there should be little concern for unwarranted use of the product by this population.

The potential benefits and risks of over-the-counter lovastatin have been carefully reviewed. The potential risks of myopathy and fetal exposure have been demonstrated to be appropriately minimized based on the results of the label comprehension and self-selection studies. Additionally, studies have demonstrated that there is minimal hepatic risk with the use of MEVACOR™ Daily by consumers with undiagnosed liver disease. An effective OTC treatment option for hypercholesterolemia is anticipated to narrow the treatment gap and to decrease the number of cardiac events on a population basis. The MEVACOR™ Daily Self-Management System which will be in place post-approval will help ensure appropriate use of the product by consumers. In summary, the potential risks of over-the-counter lovastatin have been appropriately minimized and the benefit to risk ratio supports approval of non-prescription access to lovastatin 20 mg.

E. GLOSSARY OF ABBREVIATIONS

E. Glossary of Abbreviations

AAPCC	AmericanAssociation 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
CARE	Cholesterol and Recurrent Events (pravastatin)
CHC	Chronic hepatitis C
CHD	Coronary heart disease
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
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
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

NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIDDM	Noninsulin-dependent diabetes melliuts
NNT	Number needed to treat
NOS	Not otherwise specified
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter (i.e., nonprescription)
PTY	Patient treatment years
RMRS	Regenstrief Medical Record System
4S	Scandinavian Simvastatin Survival Study (simvastatin)
SELECT	Self Evaluation of Lovastatin to Enhance Cholesterol Treatment
SOC	System organ class
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)

F. LIST OF REFERENCES

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G. APPENDICES

Appendix 1

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).

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) database 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.

Nonetheless, 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 to placebo in 8245 patients with hypercholesterolemia: total cholesterol (TC) 240 to 300 mg/dL and low-density lipoprotein cholesterol (LDL-C) >160 mg/dL. Patients with hypercholesterolemia were randomized into 5 similar groups (of 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 [2]. There was no dose titration during the study.

Clinical adverse experiences reported as possibly, probably, or definitely drug related which occurred in ≥1.0% in any one treatment group are presented in Table E-1. The percentage of patients with serious clinical adverse experiences (irrespective of drug relationship) by body system are listed in Table E-2. The safety profile of lovastatin 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. Doses up to 4 times the proposed OTC dose were well tolerated when taken for approximately 1 year. EXCEL demonstrated a clear margin of safety for the proposed OTC dose of lovastatin.

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. Lovastatin was compared to placebo for primary prevention of CHD in 6605 participants over a median duration of 5 years. The participants were predominately healthy men and women with TC and LDL-C, below average high-density lipoprotein (HDL) cholesterol, and at least one coronary heart disease (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 percentage of patients with serious adverse experiences (irrespective of drug relationship) by body system are listed in Table E-3. 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), lumbar radiculopathy (6 versus 4) and cervical radiculopathy (4 versus 5). Fewer than 4 participants per treatment group experienced other 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
Although a patient may have had two or more serious adverse experiences, the patient is counted only once in the body system total.			

Clinical 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).

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 creatine phosphokinase (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 and encompass prescription use across all doses. 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.

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 has been 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 were rhabdomyolysis (273 reports), myalgia (121 reports) and myositis (92 reports). Some cases of myopathy may have also 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

The most frequently reported serious adverse experiences were 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

The most common serious adverse experience was abnormal hepatic function (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 hepatic adverse experiences.

Investigations

The most frequently reported serious adverse experience was blood CK 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. This represents 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 have been 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 the most likely primary cause of death was selected for categorization in the table. 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.

AFCAPS/TexCAPS demonstrated that patients treated with lovastatin experienced 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 were reported to have died from cancer while or after taking lovastatin for a reporting rate of ~1 cancer per 1 million patient treatment years. The types of cancers 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 was no pattern of reporting observed for any specific cancer. Data from postapproval megatrials have shown 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 or incidence of fatal and nonfatal cancer. In the Scandinavian Simvastatin Survival Study the number of cancers was similar in the simvastatin and placebo group with no suggestion of an increase with simvastatin in cancer overall or at any particular site. In view of the limited numbers of reports and the absence of predominance of any cancer type in WAES, and the information in the published literature, there is no evidence lovastatin may induce or promote the development and progression of malignancies.

3.3 Summary of Spontaneous Reports

Review of the WAES data does not reveal an 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

Data from EXCEL, AFCAPS, the WAES database, and published clinical literature were reviewed. The data indicate that the risk of significant liver function abnormalities with lovastatin at doses of 20 mg or less is not significantly different than that observed with placebo.

4.1.2 Postapproval Clinical Studies

EXCEL

No patient in EXCEL 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 during which only 1 patient developed significant increases in transaminases.

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

Among the 6,605 participants in AFCAPS/TexCAPS, no drug-induced hepatitis was reported. Table E-7 presents the number of participants with one or more, or consecutive elevations greater than 3 x ULN in ALT, AST, or both. The category of "one or more elevations" includes participants with (1) single, (2) nonconsecutive multiple, or (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. 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 and there are no multiplicity corrections. 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.

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						

The 18 lovastatin participants and 11 placebo participants with consecutive elevations are shown in Table E-8. Of the 18 participants treated with lovastatin 11/1585 (0.7%) received 20 mg and 7/1657 (0.4%) received 40 mg. 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.

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.

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, ALT elevations subsequently 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.

There has been some discussion in the literature whether combining elevated LFTs greater than 3 x ULN (either ALT or AST) with concurrently elevated total bilirubin greater than 2 x ULN improves 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 [8] since this may signify biliary obstruction as opposed to hepatocellular injury. Three of these 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 was conducted of WAES reports with terms consistent with liver failure and clinical hepatitis. As of 01-Nov-2003 there were a total of 25 cases of hepatic failure/hepatic necrosis and 251 reports of hepatitis reported by a health care professional, Five of these reports included both adverse experiences of hepatic failure/necrosis and hepatitis. Not all of these reports could be attributed to lovastatin Even with a conservative assumption that all of 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. This indicates 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 [9]. The worldwide incidence of acute liver failure is on the order of 1 to 10 cases per million population per year [10]. Furthermore, the rate of hepatitis for nonsteroidal anti-inflammatory drugs is between 22 and 500 per 1 million patient years [11]. 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 consensus expressed in the literature is that lovastatin does not pose a significant risk of hepatic injury [6; 13]. 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 statin, 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 [6]. It is important to note that no relationship has been established between minor ALT elevations with statin use and hepatic failure [12].

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 and 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.

4.1.5 Safety of Statins in Patients With Elevated Liver Enzymes

A retrospective cohort study was conducted at the Indiana University School of Medicine [3] to assess whether patients with baseline elevations of serum transaminases had a higher risk of hepatic injury with statin treatment. Three patient cohorts were identified from data collected from a large academic medical practice. 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 categorized as mild/moderate or severe during the 6-month follow-up period. "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.

Table E-9 presents 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) and 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.

[3]

To confirm these observations, Cohort 1 was also compared with 2 additional control groups. One 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 from 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).

Atorvastatin (46%) and simvastatin (51%) were the two most commonly prescribed statins. There was no difference among the specific statins used for: 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. Additionally, there was no statistical difference in the incidence of liver enzyme elevations between 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 complied 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: proportion of patients with serum bilirubin >3 mg/dL or those who 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 [3].

These findings were consistent with those of an additional retrospective study from the Indiana University School of Medicine [14] that specifically examined the risk of hepatotoxicity with lovastatin in patients with elevated baseline transaminases. Although the lovastatin-treated patient cohorts in this study were smaller than in the first retrospective study [3] (755 lovastatin-treated vs. 1,779 statin-treated patients), liver chemistries were assessed over a longer (12-month) follow-up period. In this 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) [14]. Hyperlipidemic patients without any history of hepatitis B, hepatitis C or alcohol abuse who were prescribed lovastatin were identified. Among 135 hyperlipidemic patients with increased baseline AST or ALT who were prescribed lovastatin, 0.7% experienced significant elevations in liver biochemistries, 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 (0.3% of whom developed significant elevations in liver enzymes). 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 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 [3] and provide additional evidence that treatment with lovastatin does not increase the risk of hepatotoxicity in patients with baseline transaminase elevations [14].

4.1.6 Hepatobiliary Safety Summary

Lovastatin has been marketed for over 15 years with over 27 million patient-years of therapy. The extensive safety data from the WAES postmarketing database and the long term AFCAPS/TexCAPS study demonstrate little evidence of hepatotoxicity of the drug. Data from the EXCEL trial seemed to show a dose response in LFT elevations but doses less than 40 mg were not different from placebo. Further, two 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.

4.2 Myopathy and Rhabdomyolysis

4.2.1 Introduction

Clinical study and marketed experience with lovastatin indicate that myopathy and rhabdomyolysis occur rarely. Myopathy and rhabdomyolysis occur with all statins and the risk is dose related. 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 [15; 16; 17]. Both fibrates and niacin can cause myopathy when given alone [18; 19]. There is currently no adequate explanation for why 3 classes of lipid-lowering drugs (statins, 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 [20; 21].

Lovastatin is 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) [7]. In addition, the risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related statin [22]. Drug-drug interactions are discussed later in this Section.

4.2.2 Clinical Studies

EXCEL

As noted earlier, EXCEL was a 48-week, placebo-controlled study of lovastatin 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 lovastatin: 4 patients receiving 80 mg (0.2%), 1 patient receiving 40 mg (0.1%), and none of the 1,642 patients receiving lovastatin 20 mg. The maximum CK levels in these 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 (i.e., there were no cases of rhabdomyolysis).

As shown in Table E-10, 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.

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				
	20 mg every evening N=1642	40 mg every evening N=1645	20 mg twice daily N=1646	40 mg twice daily N=1649	Placebo N=1663
	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, there was one case of rhabdomyolysis and no cases of myopathy. 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 [61].

4.2.3 Postmarketing Spontaneous Reports

The WAES database of postmarketing adverse experience reports was searched for all reports from health care professionals 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 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.

In the remaining 148 (44%) reports no such concomitant medication was reported. 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 the 439 (81%) reports, no such concomitant medication was reported. Fatal outcome was reported in 6 (1.4%) of these 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 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 any 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

Clinical trial data suggest that the risk of myopathy increases with lovastatin dose. While the incidence of myopathy with various lovastatin doses cannot be assessed from WAES data, 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.

Table E-12 shows the number of reported cases per 100,000 patient-treatment years for the different doses of lovastatin based on estimated usage. The information shown is calculated using the number of reports without concomitant medications known to increase the risk of myopathy. It should be noted that the estimated patient-treatment years of exposure to lovastatin have not been adjusted downward to take these concomitant medications into account. Compared with the 20-mg dose, the reporting rate for rhabdomyolysis was ~12 times greater with doses ≥80 mg/day. The reporting rate for myopathy 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.

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

A number of reviews of this topic have been published in the last 3 years (2001 to 2003) [23; 24; 25; 4; 26]. 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 [1]. These publications concur that there is a risk of myopathy with any currently marketed statin, 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 statins [27; 4; 5].

The incidence of myopathy is generally similar for all currently available statins and ranges from 0.1% to 0.5% with monotherapy [28; 29]. Other reviews confirm a similar 0.1% to 0.5% incidence of myopathy (defined as symptoms plus serum CK increase of at least 10 times ULN) with lovastatin specifically [30; 31; 32; 33; 34]. Combination therapy with 2 or more lipid-lowering drugs increases the risk of myopathy to 0.5 to 2.5% [29] or to as many as 1 in 20 patients treated with combination lovastatin and gemfibrozil [35; 36; 16]. Few cases of myopathy progress to rhabdomyolysis [37], and severe rhabdomyolysis with renal failure is an even rarer occurrence [38; 39], particularly in patients receiving a lovastatin dose of 20 mg/day.

4.2.6 Myopathy Summary and Conclusions

In clinical trials, the incidence of myopathy in those receiving lovastatin 20 mg daily is similar to that reported for those taking placebo. In EXCEL, there were no cases of

myopathy with 20 mg/day, 1 case (0.03%) with 40 mg/day and 4 cases (0.2%) with 80 mg daily. In AFCAPS/TexCAPS, there were no cases of symptomatic myopathy and 1 case of rhabdomyolysis among the 3,304 (0.03%) patients on treatment with lovastatin and 2 cases of rhabdomyolysis among 3,301 (0.06%) placebo-treated participants. The number of myopathy cases in the WAES database 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. Myopathy is a symptomatic condition that can be recognized by patients and is addressed in the lovastatin OTC label. The condition virtually always resolves after discontinuation of the drug.

4.3 Drug-Drug Interactions

Lovastatin is a substrate for cytochrome P450 3A4 (CYP3A4). It is not an inhibitor or promoter of CYP3A4. It is not known to affect plasma concentrations of any other drug.

4.3.1 Pharmacokinetic Interactions with CYP3A4 Inhibitors

CYP3A4 inhibitors have been shown to increase plasma 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 showed that the risk is actually quite low. In AFCAPS/TexCAPS, concomitant use of lovastatin 20 or 40 mg and potent CYP3A4 inhibitors was not associated with increased frequencies of myopathy or myalgia (Table E-13). 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)

	Lovastatin 20 to 40 mg (N=535[‡])		Placebo (N=512[§])	
Adverse Experience	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.

4.3.2 Other Lipid-lowering Medications

Concomitant use of fibrates or niacin may increase the risk of myopathy in patients taking any statin. 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. In the case of gemfibrozil, the interaction has also 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).

It is important to note that the US product circular for Mevacor states that when taking fibrates or >1 gram/day of niacin, doses of lovastatin should not exceed 20 mg (i.e., the proposed OTC dose).

4.3.3 WAES Database

Since first approval through 1-Nov-2003 there have been 83 reports from health care professionals of "drug interactions" with CYP3A4 inhibitors, niacin and/or fibrates. There were 288 reports of myopathy where patients were reported to be taking interacting concomitant medications. Even considering the larger number of reports, given an estimated worldwide exposure to lovastatin of over 27 million patient-years, these figures give a reporting rate of ~1.0 reports per 100,000 patient-years of treatment. The data from AFCAPS/TexCAPS for these drug interactions 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.

4.3.4 Conclusions

Based on review of the available data, the following conclusions can be drawn:

- Concomitant use gemfibrozil or 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. 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

[40]. There was no attenuation in the lipid-altering efficacy of lovastatin when administered with frequently administered antihypertensive drugs. There appeared to be no clinically important deterioration in the safety and tolerability profile of lovastatin. 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 [2].

In a double-blind, placebo-controlled study of 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 [41]. 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 [42]. 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 [43]. 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 the Scandinavian Simvastatin Survival Study [44]. 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) [7]. 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. Rhabdomyolysis has also been reported in patients with severe renal impairment. 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 [45]. Changes in glomerular filtration rate over the 2-year study tended to be less in patients treated with lovastatin compared with those receiving placebo. This supports 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 [7]. Based on study information summarized in Section 4.1 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 to speak with a doctor prior to use.

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 occasionally, overt untreated hypothyroidism. Hypothyroidism is thought to account for about 2% of all cases of hyperlipidemia [46]. The effect of subclinical hypothyroidism on serum cholesterol is not large: in women, the estimated effect is ~19 mg/dL [47; 48]. 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 which are well known to most practitioners. 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, since they are more likely to be taking other medications, have complicating medical conditions, and because drug metabolism may change with age [49; 50]. 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. A placebo-controlled study of 431 patients 65 years or older found that lovastatin was extremely well tolerated [51]. A retrospective analysis of a 6-month, open-label study found that the 144 elderly (age ≥65 years) patients had a similar incidence of adverse reactions as the 343 younger patients [52].

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). 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 overdose, 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 safety of these drugs during pregnancy has not been conclusively determined [53] 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.

4.6.2 Pre-clinical Studies

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. It is notable that the doses causing skeletal malformations in animals were 700 times the maximum recommended dose in humans [54]. Furthermore, animal studies are not always predictive of either the occurrence or lack of occurrence of a teratogenic effect in human pregnancy [55].

More recent pre-clinical studies in rats showed that the fetal effects described above are caused indirectly by maternal toxicity associated with the high doses of lovastatin used in the original studies, rather than a direct result of fetal exposure [56]. These studies demonstrated 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 eliminated 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 was 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 pre-clinical neonatal toxicity study of the active metabolite of lovastatin, L-154819, was conducted in rats. A significant degree of neurological development occurs during the early postnatal period in rats 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.

4.6.3 Published Clinical Literature

Two articles [55; 57] were identified 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 [55]. 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 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 [57]. 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.

4.6.4 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 Spontaneous Reports During Marketed Use

The WAES Database was searched to identify cases entered into the database from market introduction through 01-Jun-2003 that were reported by consumers and Health Care Professionals as exposures to lovastatin during pregnancy. 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, regardless of the likelihood of a causal association. 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 prospective or retrospective. Prospective reports were those for which notice of exposure was received prior to the outcome of the pregnancy being known. Retrospective reports were 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 [58]. Prospective

reports 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.

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

Information on pregnancy outcome was available for 34 reports (50.7%) of reports. 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. There were no reports of congenital anomalies in infants among the prospective reports.

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).

Retrospective Reports

Retrospective reports are more difficult to interpret since 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. 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. No pattern of anomalies among the retrospective reports is apparent.

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.

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. Table E-18 summarizes the adverse experiences that occurred in the 1061 patients who reported taking at least one dose of lovastatin 20 mg. 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). 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 (17.3%). The most commonly reported clinical adverse experiences occurred in that category with 118 (11.1%) of patients reporting 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%).

Table E-19 summarizes the drug-related clinical adverse experiences that had ≥1% incidence in CUSTOM. 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 specific 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

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. Table E-20 summarizes clinical adverse experiences with ≥1% incidence that caused study drug discontinuation.

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.		

In addition to monitoring clinical adverse experiences, ALT levels were tested 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, 986 (92.9%) had a post-baseline laboratory test. Only 5 (0.51%) of the 986 patients had a laboratory adverse experience. 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. Three of these patients had ALT >3 x ULN; the other patient had a slightly increased ALT of 1.5 x ULN.

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 in CUSTOM was ~11%. This rate is generally consistent with that reported in the 48-week EXCEL trial for muscle symptoms: 8.3% for lovastatin 20 mg and 7.5% for placebo [59]. There were no cases of myopathy in EXCEL at the 20-mg dose. The 5.2-year AFCAPS/TexCAPS trial showed that musculoskeletal symptoms occurred during the study with similar frequency in the two treatment groups: 62.1% and 59.7% receiving lovastatin (20-40 mg/day) and placebo, respectively; p=0.563 [60]. 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 [60].

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 be aware of unexplained muscle pain may have influenced some patients to be more likely to report such pain.

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. 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 was comparable to that of placebo. Review of available safety information through 01-Nov-2003 did not identify any new safety issues.
- 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.
- 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, thyroid disease and in elderly patients.
- A review of the WAES reports of lovastatin exposure during pregnancy found no prospective reports of congenital anomalies and no pattern of anomalies among the retrospective reports. The rate of congenital anomalies in prospectively reported pregnancies was similar to the background rate. However, the number of prospectively reported cases with a known outcome was small.
- Myopathy and rhabdomyolysis occurred rarely in clinical studies and in market-use experience. The risk of lovastatin-associated myopathy increases with increasing dose of lovastatin. Myopathy is a symptomatic condition that can be recognized by patients and usually resolves after drug discontinuation.
- Concomitant use of 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. However, the associated risk of myopathy is very low with the 20-mg dose of

lovastatin, and as demonstrated by AFCAPS data remained low even with concomitant use of a strong CYP3A4 inhibitor. Concomitant use of fibrates (especially gemfibrozil) or lipid lowering doses of niacin with doses of lovastatin greater than 20 mg (i.e., greater than the proposed OTC dose) may also increase the risk of myopathy.

- Clinically apparent liver disease (hepatitis, hepatic failure) associated with lovastatin use is rare at any dose. Patients with asymptomatic, undiagnosed liver disease do not appear to be at an increased risk of developing worsening of the liver disease. 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.
- Given the large margin of safety, lovastatin 20 mg has a safety profile appropriate for use in the nonprescription setting.

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Appendix 2

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 [2] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [1]. 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 [5]. 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 [6].

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 [3]. 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

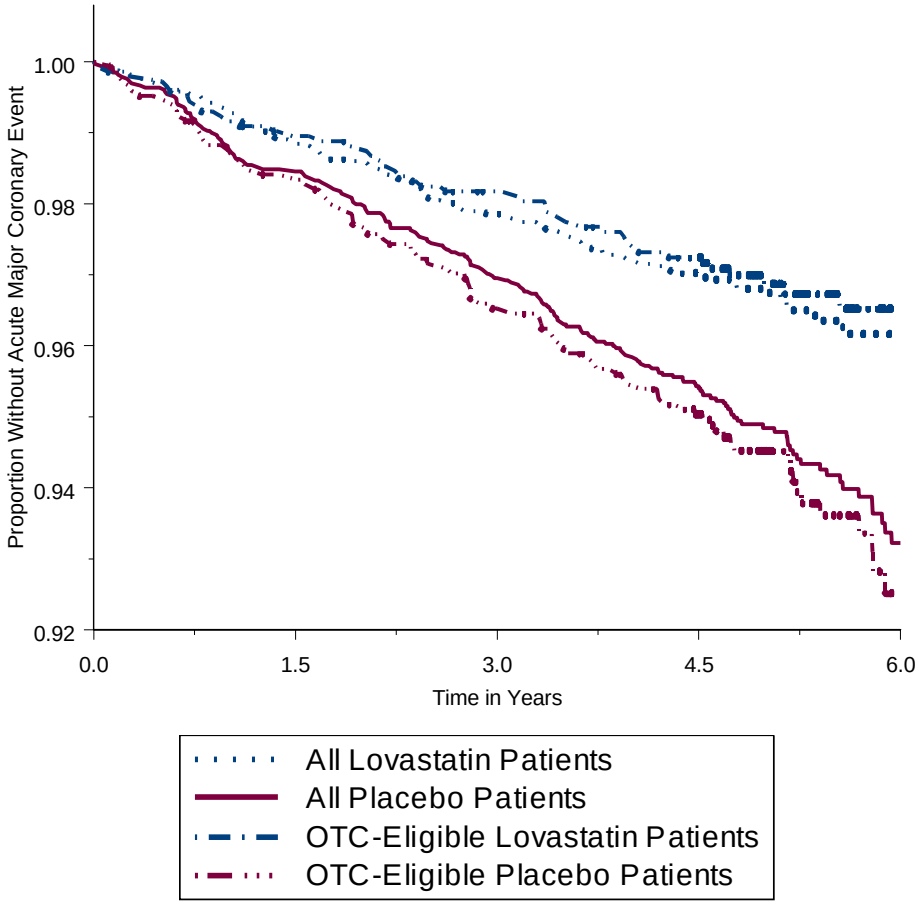


Figure C-2

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

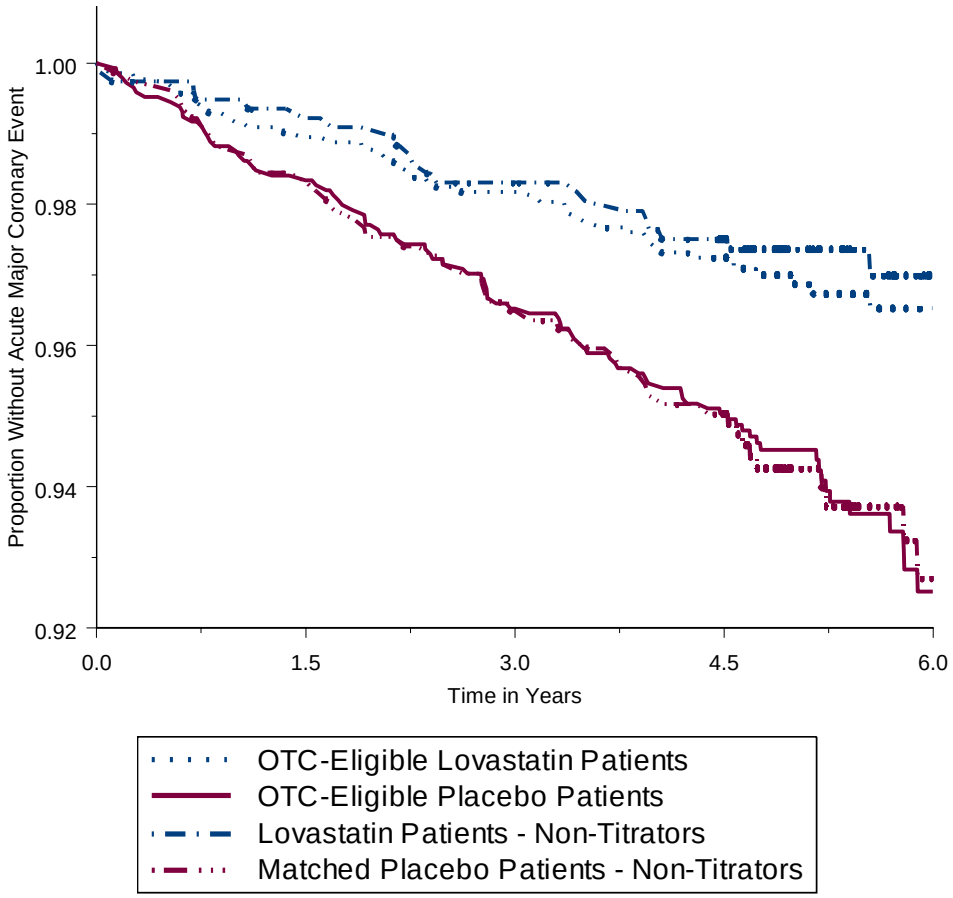
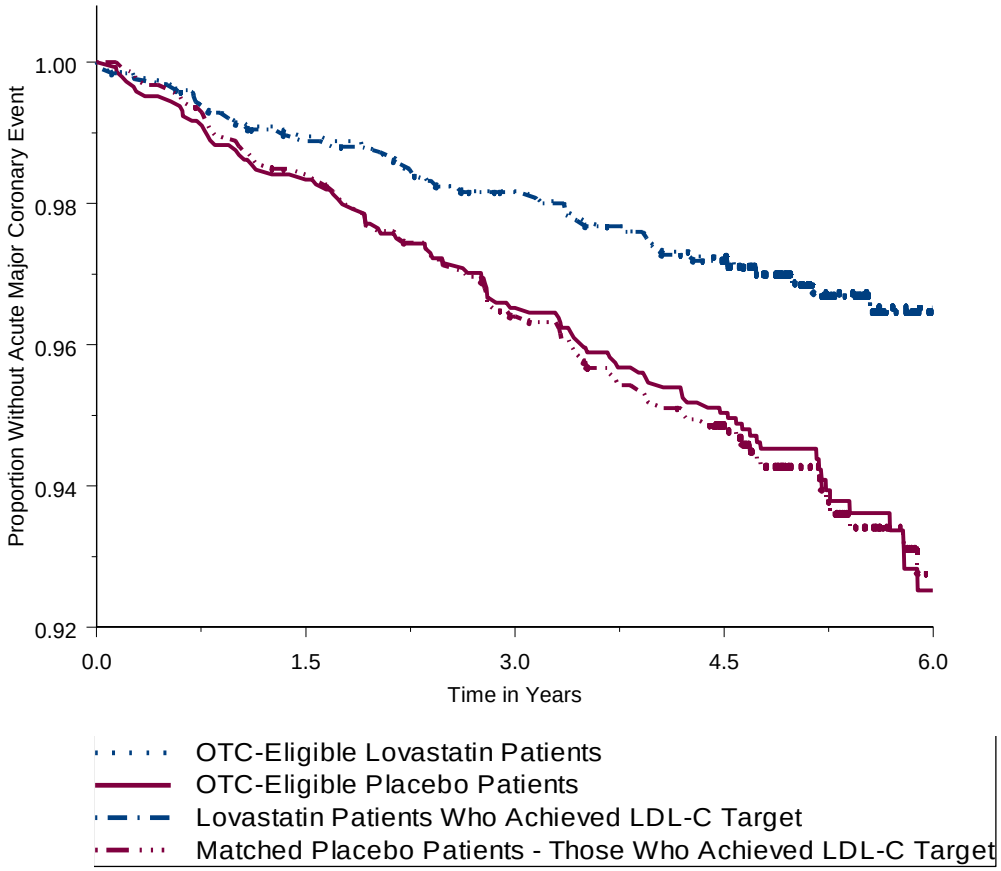


Figure C-3

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

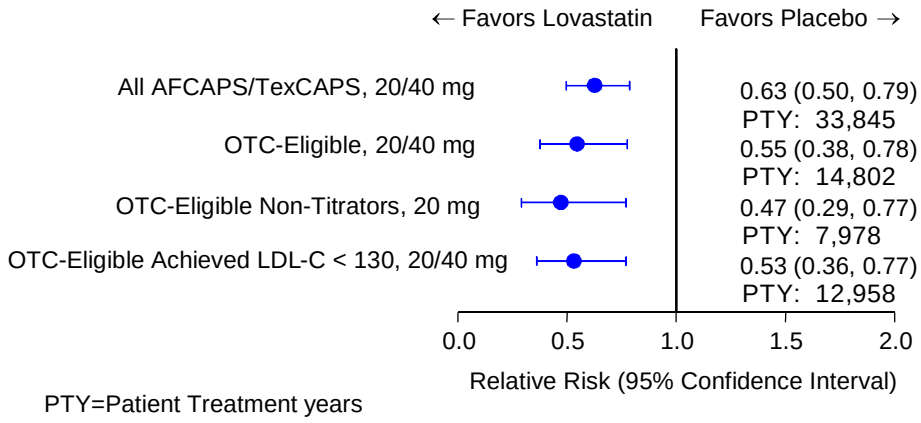


Figures C-2 and C-3 illustrate the Kaplan-Meier survival curves for each of the subgroup analyses versus the MEVACOR™ OTC-eligible cohort. These plots indicate that the Kaplan-Meier event rates for the placebo subgroups are much higher (lower probability of being CHD free) than the event rates for participants 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 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)	25th, 75th Percentiles	N	Median (mg/dL)	25th, 75th Percentiles	N	Median (mg/dL)	25th, 75th 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 ≤ 20%[4]. 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.

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.

MEVACOR™OTC (nonprescription lovastatin 20 mg)
Jan 2005 FDA Advisory Committee Background Information
Efficacy and Benefit of Lovastatin

List of References

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Appendix 3

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

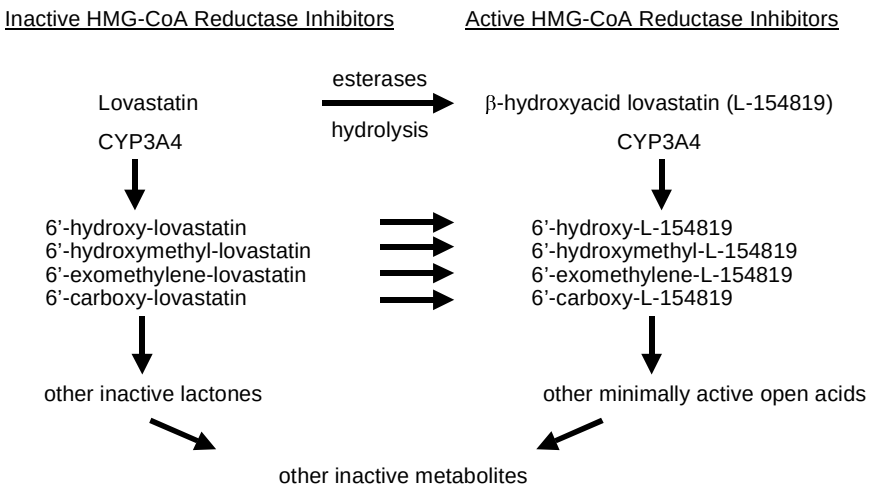


Table D-1

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 [1]. 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 [1]. 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 [2; 3].

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

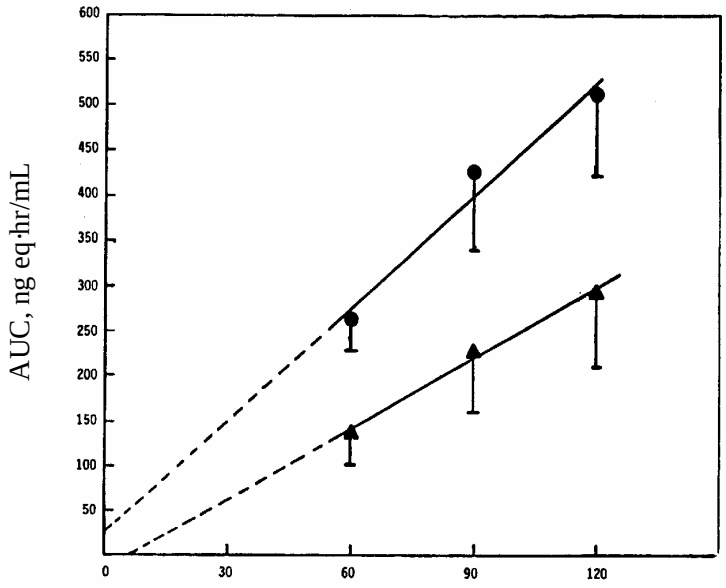
Following single oral doses of 60, 90, and 120 mg of lovastatin administered to 12 healthy male volunteers, the plasma profile parameters for HMG-CoA reductase inhibitors indicate that the pharmacokinetics of lovastatin are linear over the 60- to 120-mg dose range. A plot of the observed mean inhibitor 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 [4]. 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) [5]. 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 [6]. 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 [7]. 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) [8]. 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 [9]. 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 [10].

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. 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.

MEVACOR™OTC (nonprescription lovastatin 20 mg)
Jan 2005 FDA Advisory Committee Background Information
Pharmacokinetics and Drug Metabolism

- 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.

MEVACOR™OTC (nonprescription lovastatin 20 mg)
Jan 2005 FDA Advisory Committee Background Information
Pharmacokinetics and Drug Metabolism

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Appendix 4

PROPOSED PACKAGE LABEL (LDL)

FRONT PANEL

SCALE 100%

PROPOSED PACKAGE LABEL (LDL)

OUTSIDE PANEL

Labeling Format Information:

Fonts: Helvetica roman, bold oblique

Drug Facts:	14 pt	**Body Text Leading**:	9 pt
Header:	9 pt	**Barlines**:	2.5 pt
Body Text:	7pt	**Hairlines**	.5 pt
Avg Horizontal Scale: 100%		Avg Kerning: 0	

SCALE 100%

PROPOSED PACKAGE LABEL (LDL)

INSIDE FLAP – PANEL ON LEFT

Drug Facts (continued)

Use To help lower cholesterol, which may prevent a first heart attack.

You must follow the chart below to see if this product is right for you.

This product is ONLY for people who meet ALL OF THE REQUIREMENTS listed below. If you do not meet ALL OF THE REQUIREMENTS, you should not use this product without talking to a doctor.

AGE:
You must be:
- A woman age 55 years or older
- A man age 45 years or older

NO → STOP DO NOT USE.
Even with high cholesterol you may be at lower risk and not need this product.
Discuss with a doctor.

YES

LDL CHOLESTEROL:
Your LDL "bad" cholesterol is between 130 to 170 based on a fasting cholesterol test within the past year.

NO → STOP DO NOT USE.
If your LDL is lower you may be at lower risk and not need this product.
If your LDL is higher you may need a stronger medicine.
Discuss with a doctor.

YES

HEART DISEASE FACTORS:
You must have one or more of the following to take this medicine, because these risk factors increase your chance of having a heart attack:
- high blood pressure or taking medicine to control your blood pressure OR
- family history of heart disease: father or brother before age 55, mother or sister before age 65 OR
- smoker (smoking increases your risk) OR
- low HDL "good" cholesterol 1 to 39

NO → STOP DO NOT USE.
If you do not have any of these heart disease factors you may be at lower risk and not need this product.
Discuss with a doctor.

YES

IMPORTANT: You must also read the entire label to the right and on the bottom of the package.

Labeling Format Information:

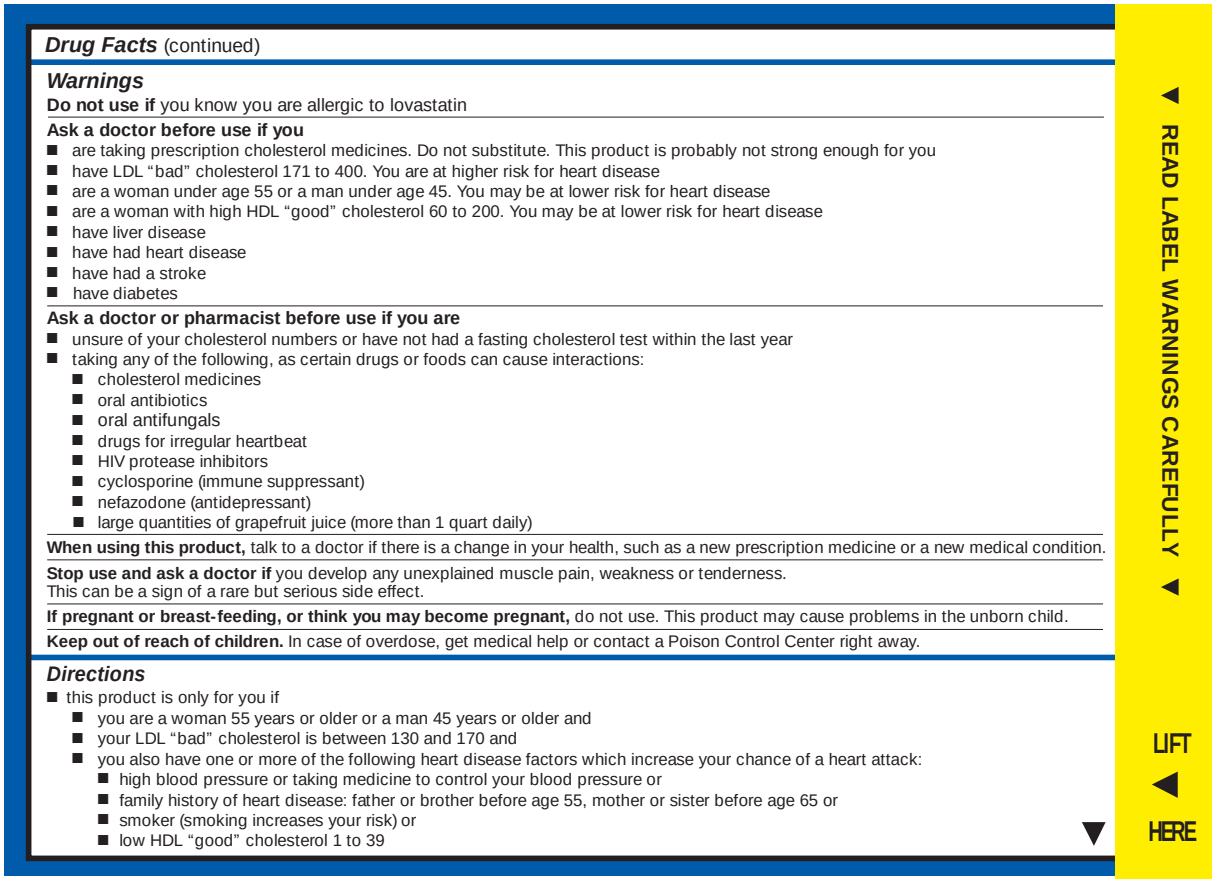
Fonts: Helvetica roman, bold oblique, black

Drug Facts:	14 pt	**Body Text Leading**:	8.5 pt
Header:	9 pt	**Barlines**:	2.5 pt
Body Text:	7 pt	**Hairlines**	.5 pt
Avg Horizontal Scale: 100%		Avg Kerning: 0	

SCALE 100%

PROPOSED PACKAGE LABEL (LDL)

INSIDE FLAP – PANEL ON RIGHT



Drug Facts (continued)

Warnings

Do not use if you know you are allergic to lovastatin

Ask a doctor before use if you

- are taking prescription cholesterol medicines. Do not substitute. This product is probably not strong enough for you
- have LDL "bad" cholesterol 171 to 400. You are at higher risk for heart disease
- are a woman under age 55 or a man under age 45. You may be at lower risk for heart disease
- are a woman with high HDL "good" cholesterol 60 to 200. You may be at lower risk for heart disease
- have liver disease
- have had heart disease
- have had a stroke
- have diabetes

Ask a doctor or pharmacist before use if you are

- unsure of your cholesterol numbers or have not had a fasting cholesterol test within the last year
- taking any of the following, as certain drugs or foods can cause interactions:
  - cholesterol medicines
  - oral antibiotics
  - oral antifungals
  - drugs for irregular heartbeat
  - HIV protease inhibitors
  - cyclosporine (immune suppressant)
  - nefazodone (antidepressant)
  - large quantities of grapefruit juice (more than 1 quart daily)

When using this product, talk to a doctor if there is a change in your health, such as a new prescription medicine or a new medical condition.

Stop use and ask a doctor if you develop any unexplained muscle pain, weakness or tenderness. This can be a sign of a rare but serious side effect.

If pregnant or breast-feeding, or think you may become pregnant, do not use. This product may cause problems in the unborn child.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- this product is only for you if
  - you are a woman 55 years or older or a man 45 years or older and
  - your LDL "bad" cholesterol is between 130 and 170 and
  - you also have one or more of the following heart disease factors which increase your chance of a heart attack:
    - high blood pressure or taking medicine to control your blood pressure or
    - family history of heart disease: father or brother before age 55, mother or sister before age 65 or
    - smoker (smoking increases your risk) or
    - low HDL "good" cholesterol 1 to 39

▼ READ LABEL WARNINGS CAREFULLY ▼

LIFT ◀ HERE

Labeling Format Information:

Fonts: Helvetica roman, bold oblique, black

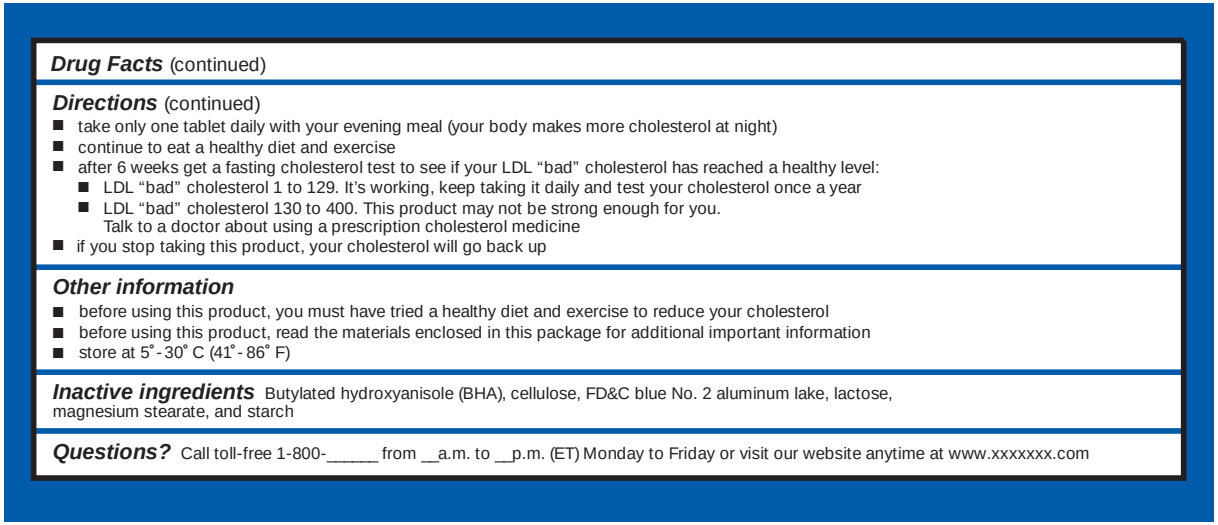
Drug Facts:	14 pt	**Body Text Leading**:	7.5 pt
Header:	9 pt	**Bullets**	6 pt
Subheader:	7.5 pt	**Barlines**:	2.5 pt
Body Text:	7 pt	**Hairlines**	.5 pt

Avg Horizontal Scale: 100% Avg Kerning: 0

SCALE 100%

PROPOSED PACKAGE LABEL (LDL)

BOTTOM PANEL



Drug Facts (continued)

Directions (continued)

- take only one tablet daily with your evening meal (your body makes more cholesterol at night)
- continue to eat a healthy diet and exercise
- after 6 weeks get a fasting cholesterol test to see if your LDL "bad" cholesterol has reached a healthy level:
  - LDL "bad" cholesterol 1 to 129. It's working, keep taking it daily and test your cholesterol once a year
  - LDL "bad" cholesterol 130 to 400. This product may not be strong enough for you. Talk to a doctor about using a prescription cholesterol medicine
- if you stop taking this product, your cholesterol will go back up

Other information

- before using this product, you must have tried a healthy diet and exercise to reduce your cholesterol
- before using this product, read the materials enclosed in this package for additional important information
- store at 5˚- 30˚ C (41˚- 86˚ F)

Inactive ingredients Butylated hydroxyanisole (BHA), cellulose, FD&C blue No. 2 aluminum lake, lactose, magnesium stearate, and starch

Questions? Call toll-free 1-800-_____ from __a.m. to __p.m. (ET) Monday to Friday or visit our website anytime at www.xxxxxxx.com

Labeling Format Information:

Fonts: Helvetica roman, bold oblique, black

Drug Facts:	14 pt	**Body Text Leading**:	7.5 pt
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Body Text:	7 pt	**Hairlines**	.5 pt

Avg Horizontal Scale: 100% Avg Kerning: 0

SCALE 100%

FRONT

PACKAGE INSERT

IMPORTANT INFORMATION ABOUT MEVACOR™ Daily (Lovastatin 20 mg).
PLEASE READ THIS PACKAGE INSERT AND SAVE FOR FUTURE USE.

MEVACOR™
Lovastatin 20 mg
CHOLESTEROL REDUCER
Daily

What is MEVACOR™ Daily?
MEVACOR™ Daily contains an ingredient that has been used for over 20 years by millions of people to lower their cholesterol. MEVACOR™ Daily 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™ Daily work?
MEVACOR™ Daily helps your liver produce less cholesterol. As a result, MEVACOR™ Daily reduces the level of LDL "bad" cholesterol in the blood. Because your body makes cholesterol every day, you need to take MEVACOR™ Daily every day to control it. With continued use, MEVACOR™ Daily can help you keep your cholesterol down, which could lead to a healthier heart.

What are the side effects of MEVACOR™ Daily?
The active ingredient in MEVACOR™ Daily 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™ Daily, stop use and talk to your doctor right away.

- **Stop using and tell your doctor right away if you develop new or unusual muscle pain, tenderness or weakness that you can't explain (especially if you have a fever or feel ill). This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage. This side effect can occur even if you have been on MEVACOR™ Daily for a long period of time.**

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™ Daily, you should carefully read the back of the package and this package insert to determine if MEVACOR™ Daily 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™ Daily 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.

8¼"

6¾"

Labeling Format Information:

Fonts: Helvetica roman, bold, black, and bold italic

Subheads:	8.5 pt
Text:	8.5 pt
Text Leading:	9.25 pt
Bullets:	8.5 pt
Hairlines:	.5 pt

Avg Horizontal Scale: 80% Avg Kerning: 0

SCALE 100%

BACK

PACKAGE INSERT

Warnings

Do not use if you know you are allergic to lovastatin

Stop using and tell your doctor right away if you develop new or unusual muscle pain, tenderness or weakness that you can't explain (especially if you have a fever or feel ill). This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage. This side effect can occur even if you have been on MEVACOR™ Daily for a long period of time.

Ask a doctor before use if you

- are taking prescription cholesterol medicines. Do not substitute. This product is probably not strong enough for you
- have LDL "bad" cholesterol 171 to 400. You are at higher risk for heart disease
- are a woman under age 55 or a man under age 45. You may be at lower risk for heart disease
- are a woman with high HDL "good" cholesterol 60 to 200. You may be at lower risk for heart disease
- have liver disease
- have had heart disease
- have had a stroke
- have diabetes

Ask a doctor or pharmacist before use if you are

- unsure of your cholesterol numbers or have not had a fasting cholesterol test within the last year
- taking any of the following **(because certain drugs or foods can cause interactions and may increase the risk of muscle side effects):**
  - cholesterol medicines
  - oral antibiotics
  - oral antifungals
  - drugs for irregular heartbeat
  - HIV protease inhibitors
  - cyclosporine (immune suppressant)
  - nefazodone (antidepressant)
  - large quantities of grapefruit juice (more than 1 quart daily)

When using this product, talk to a doctor if there is a change in your health, such as a new prescription medicine or a new medical condition.

If pregnant or breast-feeding, or think you may become pregnant, do not use. This product may cause problems in the unborn child.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- this product is only for you if
  - you are a woman 55 years or older or a man 45 years or older and
  - your LDL "bad" cholesterol is between 130 and 170 and
  - you also have one or more of the following heart disease factors which increase your chance of a heart attack:
    - high blood pressure or taking medicine to control your blood pressure or
    - family history of heart disease: father or brother before age 55, mother or sister before age 65 or
    - smoker (smoking increases your risk) or
    - low HDL "good" cholesterol 1 to 39
- take only one tablet daily with your evening meal (your body makes more cholesterol at night)
- continue to eat a healthy diet and exercise
- after 6 weeks get a fasting cholesterol test to see if your LDL "bad" cholesterol has reached a healthy level:
  - LDL "bad" cholesterol 1 to 129. It's working, keep taking it daily and test your cholesterol once a year
  - LDL "bad" cholesterol 130 to 400. This product may not be strong enough for you. Talk to a doctor about using a prescription cholesterol medicine
- if you stop taking this product, your cholesterol will go back up

Other information

- before using this product, you must have tried a healthy diet and exercise to reduce your cholesterol
- before using this product, read the materials enclosed in this package for additional important information
- store at 5°- 30° C (41°- 86° F)

Inactive ingredients Butylated hydroxyanisole (BHA), cellulose, FD&C blue No. 2 aluminum lake, lactose, magnesium stearate, and starch

Questions? Call toll-free 1-800-_____ from __a.m. to __p.m. (ET) Monday to Friday or visit our website anytime at www.xxxxxxx.com

8¼"

6¾"

Labeling Format Information:

Fonts: Helvetica roman, bold, black, and bold italic

Heads:	10.5 pt	**Bullets**:	8.5 pt
Subheads:	8.5 pt	**Hairlines**:	.5 pt
Text:	8.5 pt		
Text Leading:	9.25 pt		

Avg Horizontal Scale: 80% Avg Kerning: 0

SCALE 100%

HEART HEALTHY LIVING GUIDE

Visit us often
at www.MevacorDaily.com

Questions?
Call a Product Specialist
at 1-800-XXX-XXXX

MEVACOR™
Lovastatin 20 mg Daily

Get your LDL cholesterol to 129 or below... and keep it down.

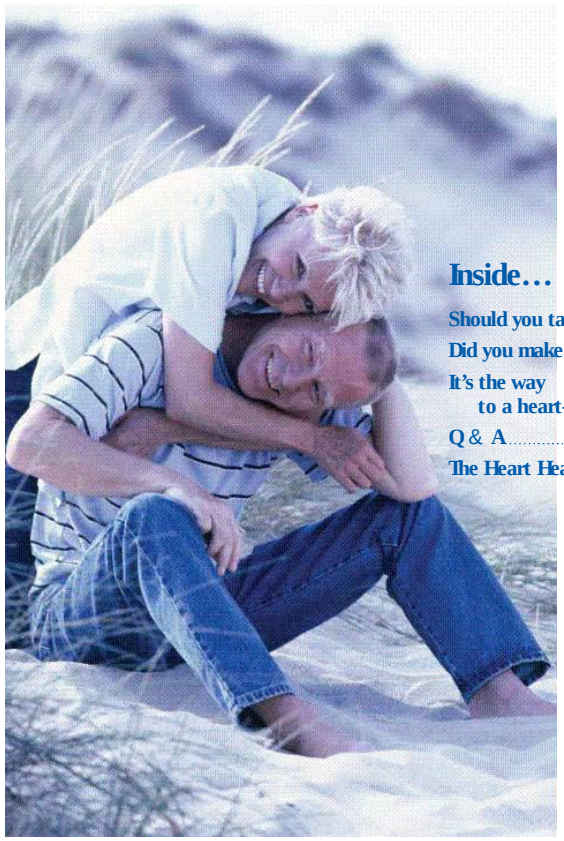
your guide to Heart Healthy Living

MEVACOR™
Lovastatin 20 mg Daily

Get your LDL cholesterol to 129 or below... and keep it down.

SCALE: 100%

HEART HEALTHY LIVING GUIDE



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™ Daily can help to reduce it.

The way to a heart-healthy life.

Taking control of your heart health includes lifestyle changes and MEVACOR™ Daily. 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™ Daily can work for you.

SCALE: 100%

HEART HEALTHY LIVING GUIDE

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™ Daily Heart Health Program!**

If you have already referred to the Quick Start Guide and enrolled in the MEVACOR™ Daily 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.

You must follow the chart below to see if this product is right for you.

This product is ONLY for people who meet ALL OF THE REQUIREMENTS listed below. If you do not meet ALL OF THE REQUIREMENTS, you should not use this product without talking to a doctor.

AGE:
You must be:
- A woman age 55 years or older
- A man age 45 years or older

NO → STOP **DO NOT USE.** Even with high cholesterol you may be at lower risk and not need this product. Discuss with a doctor.

YES ↓

LDL CHOLESTEROL:
Your LDL "bad" cholesterol is between 130 to 170 based on a fasting cholesterol test within the past year.

NO → STOP **DO NOT USE.** If your LDL is **lower** you may be at lower risk and not need this product. If your LDL is **higher** you may need a stronger medicine. Discuss with a doctor.

YES ↓

HEART DISEASE FACTORS:
You **must have one or more** of the following to take this medicine, because these risk factors increase your chance of having a heart attack:
- high blood pressure or taking medicine to control your blood pressure **OR**
- family history of heart disease: father or brother before age 55, mother or sister before age 65 **OR**
- smoker (smoking increases your risk) **OR**
- low HDL "good" cholesterol 1 to 39

NO → STOP **DO NOT USE.** If you do not have any of these heart disease factors you may be at lower risk and not need this product. Discuss with a doctor.

YES ↓

See package insert for additional information to be sure MEVACOR™ Daily is right for you.

SCALE: 100%

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™ Daily 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™ Daily. *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.MevacorDaily.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. 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.

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. Test in your own home.
- If you prefer, order your home test and perform the cholesterol test yourself.
- Mail in your $10 payment (or $5 payment and your $5 coupon†) to: At-Home Test, P.O. Box 625, Horsham, PA 19044
- Make check payable to: BIOSAFE
- Please allow 1 week for delivery of your home test kit. (*PLEASE NOTE: Home test requires you prick your finger to draw blood. Results mailed to you within 1 week of receipt of your test sample.*)

Questions?

Contact MEVACOR™ Daily Customer Service
at 1-800-XXX-XXXX or visit www.MevacorDaily.com.
Your MEVACOR™ Daily Product Specialist can recommend convenient testing options near you.

* Some states do not allow laboratory work to be done without a doctor's prescription.

† See pgs 22 & 23 for information on how to enroll in the Heart Health Program. You'll receive a $5 coupon for savings on a cholesterol test.

SCALE: 100%

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™ Daily 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 taking MEVACOR™ Daily.

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™ Daily 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™ Daily 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.

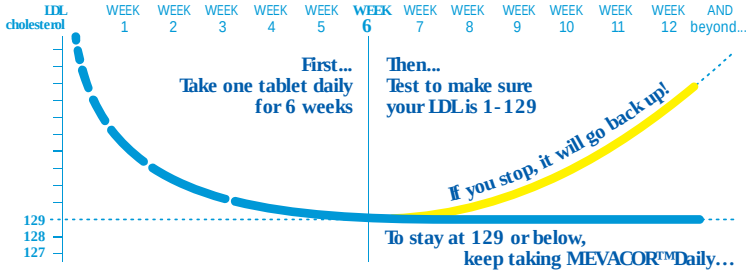
Get your LDL down to 1-129… and keep it down!

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™ Daily 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™ Daily every day.

You can't change the fact that your body makes too much LDL "bad" cholesterol, but by taking MEVACOR™ Daily every day 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.

SCALE: 100%

It's the way to a heart-healthy life.

4 Two things to watch for... every day.

Stop using and tell your doctor right away if you develop new or unusual muscle pain, tenderness or weakness that you can't explain (especially if you have a fever or feel ill). This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage. This side effect can occur even if you have been on MEVACOR™ Daily for a long period of time.

See package insert for additional information.

Certain prescription medicines may interact with MEVACOR™ Daily and may increase the risk of muscle side effects.

If you are prescribed any new medicines, remember to tell your doctor or pharmacist you are taking MEVACOR™ Daily.

See package insert for additional information.

If there is a change in your health...

Talk to your doctor.

As you already know, MEVACOR™ Daily is not meant for people with diabetes or those who have had a stroke or a heart attack.

If, while you are taking MEVACOR™ Daily, you are diagnosed with a new medical condition, or you are prescribed a new medicine, tell your doctor you are taking MEVACOR™ Daily.

Remember...you should not be taking MEVACOR™ Daily if:

- You discover you have an allergy to lovastatin, the active ingredient in MEVACOR™ Daily, or the inactive ingredients in this medicine, as listed on the package.
- You are, or plan to become, pregnant. Or, you start breast-feeding.

SCALE: 100%

It's the way to a heart-healthy life.

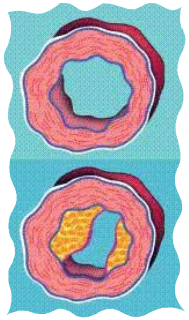
Understanding cholesterol…

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.



A normal artery

An artery with a buildup of plaque

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™ Daily 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™ Daily 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.

SCALE: 100%

HEART HEALTHY LIVING GUIDE

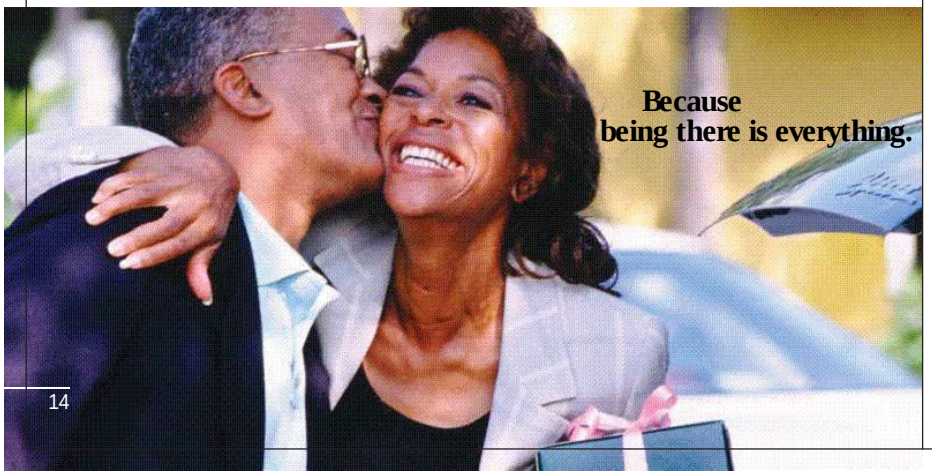
It's the way to a heart-healthy life.

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™ Daily, 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™ Daily every day as part of a cholesterol management program that includes a healthy diet and regular exercise.



MEVACOR™ Daily can make a difference.

The ingredient in MEVACOR™ Daily has been prescribed by doctors for over 20 years. Millions of people have used it successfully to lower and control their cholesterol.

Take 1 tablet daily.

It's best to take MEVACOR™ Daily with your evening meal. That's because your body produces more cholesterol at night. MEVACOR™ Daily helps to control the amount of LDL cholesterol produced by your liver.

If you miss a dose, don't double up.

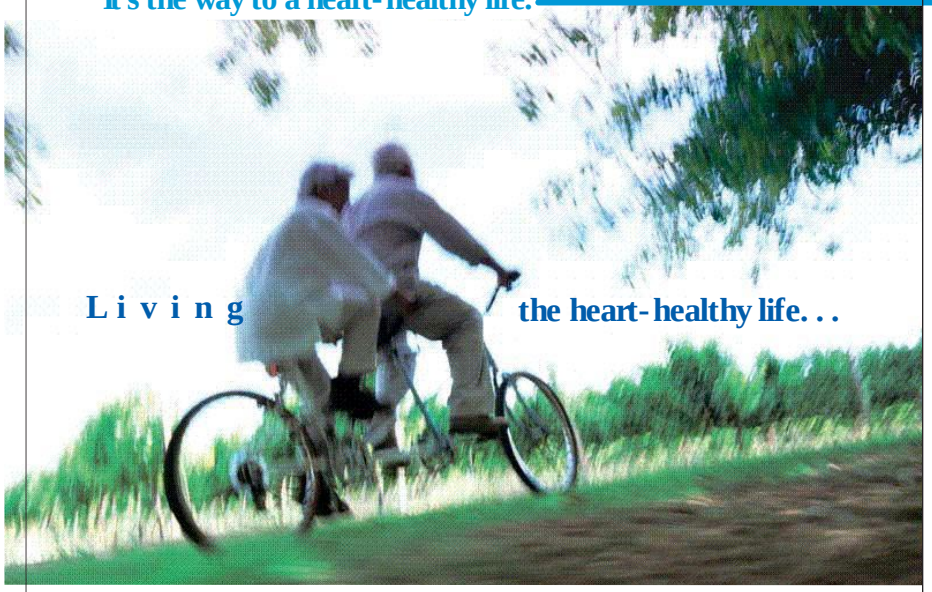
If you forget to take your MEVACOR™ Daily, DO NOT try to "make up" by taking a double dose the next day. Just wait for the next night and resume your normal pattern.

Remember, in order for MEVACOR™ Daily 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.

SCALE: 100%

HEART HEALTHY LIVING GUIDE

It's the way to a heart-healthy life.



The role of diet and exercise.

MEVACOR™ Daily 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™ Daily every day, 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™ Daily every day!

SCALE: 100%

Q&A

Frequently Asked Questions About MEVACOR™ Daily

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™ Daily 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 three important numbers:

- Total cholesterol
- LDL cholesterol
- HDL cholesterol

Q: After checking all my numbers and the rest of the information on the package, I've determined that MEVACOR™ Daily 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™ Daily 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™ Daily.

Q: Will I feel better if I take MEVACOR™ Daily?

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™ Daily, along with a healthy diet and exercise, can help lower your LDL cholesterol and keep it down.

Q: Once I start taking MEVACOR™ Daily, can I eat whatever I want?

A: No. MEVACOR™ Daily 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.

SCALE: 100%

Q&A

Q: Why isn't MEVACOR™ Daily right for everyone?

A: MEVACOR™ Daily is appropriate only for those people who meet all of the conditions listed on 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™ Daily.

Q: Once I get my LDL cholesterol down to 129 or below, why can't I stop taking MEVACOR™ Daily?

A: If you stop taking MEVACOR™ Daily, your LDL cholesterol will go back up. High cholesterol isn't a condition that can be "cured", but it can be managed. MEVACOR™ Daily, 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™ Daily. 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™ Daily. Remember, getting "close" doesn't count. Your LDL must be 1-129 to keep taking MEVACOR™ Daily. After 6 weeks, MEVACOR™ Daily 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 20 mg Daily

SCALE: 100%

HEART HEALTHY LIVING GUIDE

Important…

Enroll in the MEVACOR™ Daily Heart Health Program!

MEVACOR™ Lovastatin 20 mg Daily Heart•Health PROGRAM

It's the way to a heart-healthy life.

The MEVACOR™ Daily 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.MevacorDaily.com or**
- **USE the enclosed pre-paid postcard**

Your Heart Health Program benefits begin immediately... if you haven't enrolled yet, do it now!

Over $25 in savings!

FREE bottle of MEVACOR™ Daily

$5 savings on a cholesterol test.

FREE DVD with more information about controlling your cholesterol.

FREE American Heart Association cookbook.

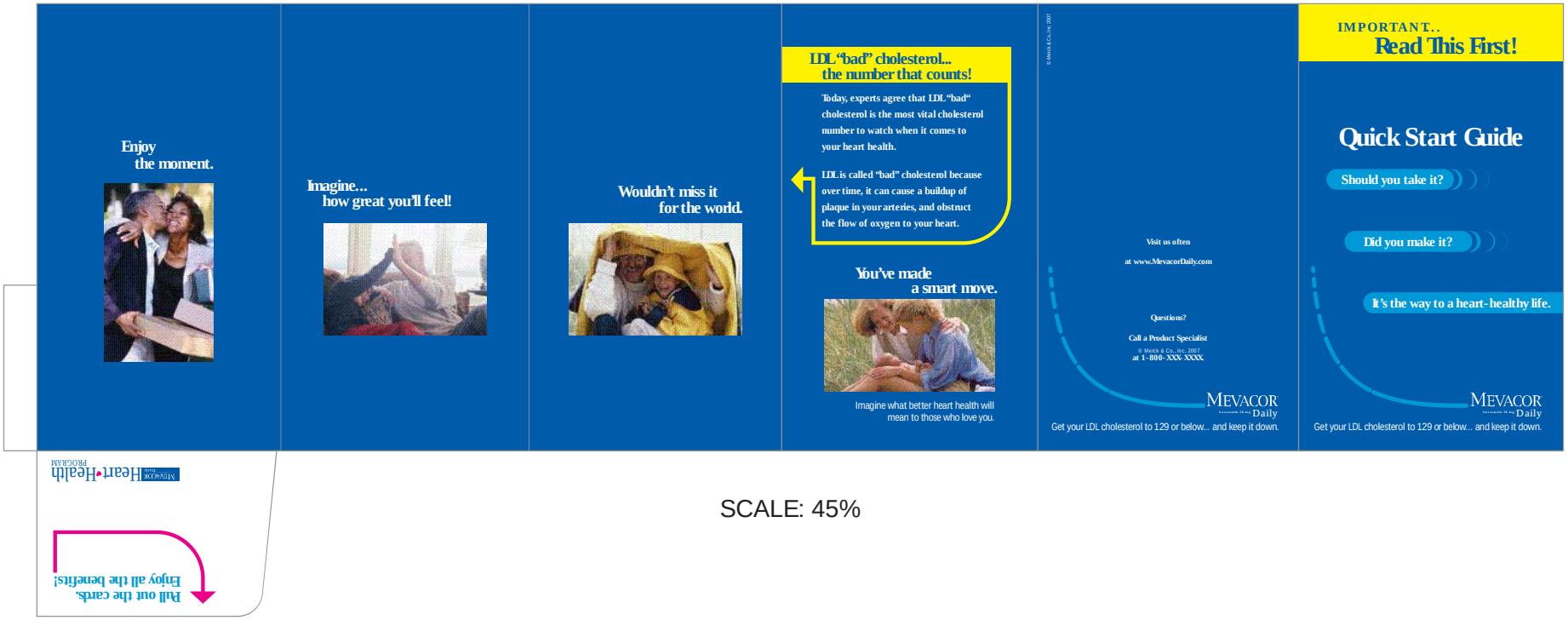
FREE reminders and bulletins to help keep you on track.

Plus... much more!

FREE when you enroll!

SCALE: 100%

QUICK START GUIDE



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Should you take it?

1 Double-check to make sure it's right for you.

You must follow the chart below to see if this product is right for you.

This product is ONLY for people who meet ALL OF THE REQUIREMENTS listed below. If you do not meet ALL OF THE REQUIREMENTS, you should not use this product without talking to a doctor.

AGE:
You must be:
- A woman age 55 years or older
- A man age 45 years or older

NO → STOP — DO NOT USE. Discuss with a doctor.

YES

LDL CHOLESTEROL:
Your LDL "bad" cholesterol is between 130 to 170 based on a fasting cholesterol test within the past year.

NO → STOP — DO NOT USE. Discuss with a doctor.

YES

HEART DISEASE FACTORS:
You **must have one or more** of the following to take this medicine, because these risk factors increase your chance of having a heart attack:
- high blood pressure or taking medicine to control your blood pressure **OR**
- family history of heart disease: father or brother before age 55, mother or sister before age 65 **OR**
- smoker (smoking increases your risk) **OR**
- low HDL "good" cholesterol 1 to 39

NO → STOP — DO NOT USE. Discuss with a doctor.

YES

See package insert for additional information to be sure MEVACOR™ Daily is right for you.

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™ Daily 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™ Daily.

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.MevacorDaily.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™ Daily 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™ Daily.**
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™ Daily 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™ Daily 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.

WARNING 1

Stop using and tell your doctor right away if you develop new or unusual muscle pain, tenderness or weakness that you can't explain (especially if you have a fever or feel ill). This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage. This side effect can occur even if you have been on MEVACOR™ Daily for a long period of time.

WARNING 2

Certain prescription medicines may interact with MEVACOR™ Daily and may increase the risk of muscle side effects.
If you are prescribed any new medicines, remember to tell your doctor or pharmacist you are taking MEVACOR™ Daily.

5 Important… enroll in the Heart Health Program!

Enroll now... get your next bottle FREE!

The MEVACOR™ Daily 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.MevacorDaily.com or**
- **USE the enclosed pre-paid postcard**

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$5 savings on a cholesterol test.
FREE 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!

6 Tell your doctor and pharmacist & start your program today!

3 Tip Card Inserts go in this pocket.

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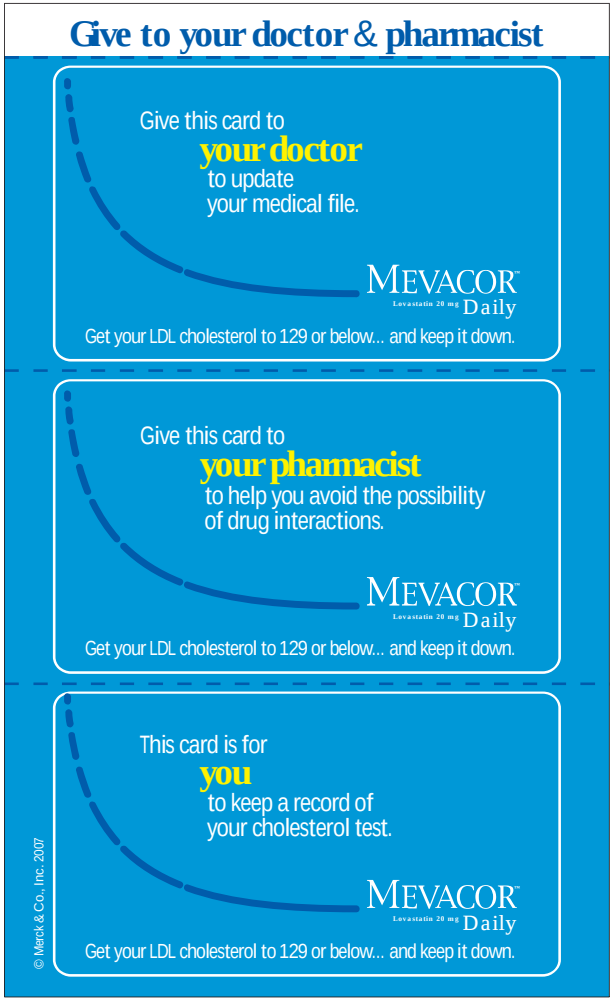
TIP CARD INSERT 1



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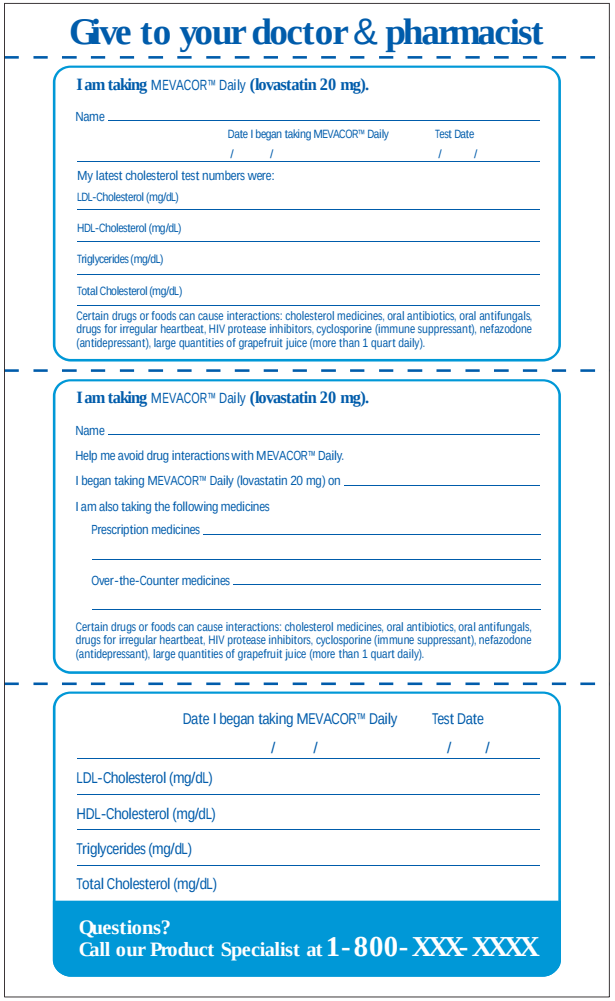

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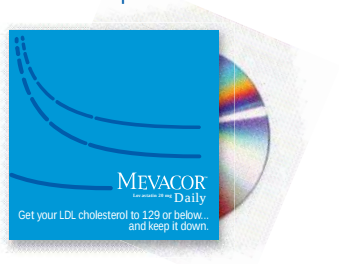
TIP CARD INSERT 2

Send for a FREE DVD

MAIL-IN CERTIFICATE	EXPIRES XX/XX/XXXX

If you'd like to know more... FREE DVD.

We'll send you a free DVD with more information about controlling your cholesterol with MEVACOR™ Daily... absolutely FREE. Just complete the information below.



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ANYTOWN, USA 12345-6789

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TIP CARD INSERT 3

Enroll in the program now!

Please contact me about enrolling in the MEVACOR™ Daily Heart Health Program. Enrollment entitles me to:

- **FREE** bottle of MEVACOR™ Daily.
- **$5 savings** on a cholesterol test.
- **FREE** American Heart Association cookbook.
- **FREE** reminders and bulletins to help keep me on track.
- **FREE** 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 _____

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NOTE: Offer good only in U.S.A. and APO/FPO addresses. This request form may not be mechanically reproduced. LIMIT ONE MEVACOR™ Daily 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 DVD.

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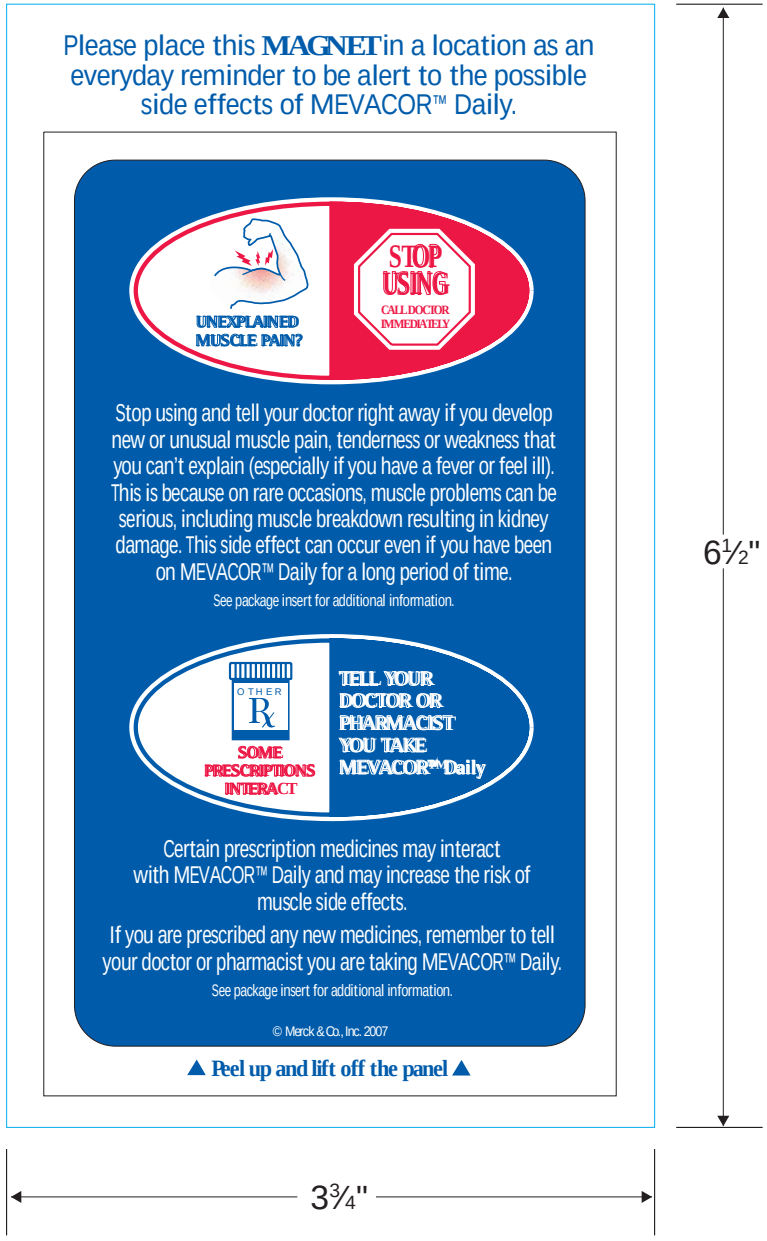


Appendix 5

Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

THE THIRD REPORT OF THE Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) constitutes the National Cholesterol Education Program's (NCEP's) updated clinical guidelines for cholesterol testing and management. The full ATP III document is an evidence-based and extensively referenced report that provides the scientific rationale for the recommendations contained in the executive summary. ATP III builds on previous ATP reports and expands the indications for intensive cholesterol-lowering therapy in clinical practice. It should be noted that these guidelines are intended to inform, not replace, the physician's clinical judgment, which must ultimately determine the appropriate treatment for each individual.

BACKGROUND

The third ATP report updates the existing recommendations for clinical management of high blood cholesterol. The NCEP periodically produces ATP clinical updates as warranted by advances in the science of cholesterol management. Each of the guideline reports—ATP I, II, and III—has a major thrust. ATP I outlined a strategy for primary prevention of coronary heart disease (CHD) in persons with high levels of low-density lipoprotein (LDL) cholesterol (≥160 mg/dL) or those with borderline high LDL cholesterol (130-159 mg/dL) and multiple (2+) risk factors. ATP II affirmed the importance of this approach and added a new feature: the intensive management of LDL cholesterol in persons with established CHD. For patients with CHD, ATP II set a new, lower LDL cholesterol goal of ≤100 mg/dL. ATP III adds a call for more intensive LDL-lowering therapy in certain groups of people, in accord with recent clinical trial evidence, but its core is based on ATP I and ATP II. Some of the important features shared with previous reports are shown in **Table A** in the **APPENDIX**.

See also p 2508 and Patient Page.

While ATP III maintains attention to intensive treatment of patients with CHD, its major new feature is a focus on primary prevention in persons with multiple risk factors. Many of these persons have a relatively high risk for CHD and will benefit from more intensive LDL-lowering treatment than recommended in ATP II. **TABLE 1** shows the new features of ATP III. (Note: To convert cholesterol to mmol/L, divide values by 38.7).

LDL CHOLESTEROL: THE PRIMARY TARGET OF THERAPY

Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolemia indicate that elevated LDL cholesterol is a major cause of CHD. In addition, recent clinical trials robustly show that LDL-lowering therapy reduces risk for CHD. For these reasons, ATP III continues to identify elevated LDL cholesterol as the primary target of cholesterol-lowering therapy. As a result, the primary goals of therapy and the cutpoints for initiating treatment are stated in terms of LDL.

RISK ASSESSMENT: FIRST STEP IN RISK MANAGEMENT

A basic principle of prevention is that the intensity of risk-reduction therapy should be adjusted to a person's absolute risk. Hence, the first step in selection of LDL-lowering therapy is to assess a person's risk status. Risk assessment requires measurement of LDL cholesterol as part of lipoprotein analysis and identification of accompanying risk determinants.

In all adults aged 20 years or older, a fasting lipoprotein profile (total cholesterol, LDL cholesterol, high-density lipoprotein [HDL] cholesterol, and triglyceride) should be obtained once every 5 years. If the testing opportunity is nonfasting, only the values for total choles-

Corresponding Author and Reprints: James I. Cleeman, MD, National Cholesterol Education Program, National Heart, Lung, and Blood Institute (NHLBI), 31 Center Dr, Room 4A16, MSC 2480, Bethesda, MD 20892-2480 (e-mail: cleemanj@nih.gov).

The Full Report of ATP III is available online on the NHLBI Web site at www.nhlbi.nih.gov.

Members of the NCEP Expert Panel are listed at the end of this article.

terol and HDL cholesterol will be usable. In such a case, if total cholesterol is ≥200 mg/dL or HDL is <40 mg/dL, a follow-up lipoprotein profile is needed for appropriate management based on LDL. The relationship between LDL cholesterol levels and CHD risk is continuous over a broad range of LDL levels from low to high. Therefore, ATP III adopts the classification of LDL cholesterol levels shown in **TABLE 2**, which also shows the classification of total and HDL cholesterol levels.

Risk determinants in addition to LDL cholesterol include the presence or absence of CHD, other clinical forms of atherosclerotic disease, and the major risk factors other than LDL (**TABLE 3**). (LDL is not counted among the risk factors in Table 3 because the purpose of counting those risk factors is to modify the treatment of LDL.) Based on these other risk determinants, ATP III identifies 3 categories of risk that modify the goals and modalities of LDL-lowering therapy. **TABLE 4** defines these categories of risk and shows corresponding LDL cholesterol goals.

The category of highest risk consists of CHD and CHD risk equivalents. The latter carry a risk for major coronary events equal to that of established CHD, ie, >20% per 10 years (ie, more than 20 of 100 such individuals will develop CHD or have a recurrent CHD event within 10 years). CHD risk equivalents comprise:

- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease)
- Diabetes
- Multiple risk factors that confer a 10-year risk for CHD >20%.

Diabetes counts as a CHD risk equivalent because it confers a high risk of new CHD within 10 years, in part because of its frequent association with multiple risk factors. Furthermore, because persons with diabetes who experience a myocardial infarction have an unusually high death rate either immediately or in the long term, a more intensive prevention strategy is warranted. Persons with CHD or CHD risk equivalents have the lowest LDL cholesterol goal (<100 mg/dL).

The second category consists of persons with multiple (2+) risk factors in whom 10-year risk for CHD is ≤20%. Risk is estimated from Framingham risk scores (see Appendix). The major risk factors, exclusive of elevated LDL cholesterol, are used to define the presence of multiple risk factors that modify the goals and cutpoints for LDL-lowering treatment, and these are listed in Table 3. The LDL cholesterol goal for persons with multiple (2+) risk factors is <130 mg/dL.

The third category consists of persons having 0-1 risk factor; with few exceptions, persons in this category have a 10-year risk <10%. Their LDL cholesterol goal is <160 mg/dL.

Table 1. New Features of ATP III*

Focus on Multiple Risk Factors
• Raises persons with diabetes without CHD, most of whom have multiple risk factors, to the risk level of CHD risk equivalent
• Uses Framingham projections of 10-year absolute CHD risk (ie, the percent probability of having a CHD event in 10 years) to identify certain patients with multiple (2+) risk factors for more intensive treatment
• Identifies persons with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle changes
Modifications of Lipid and Lipoprotein Classification
• Identifies LDL cholesterol <100 mg/dL as optimal
• Raises categorical low HDL cholesterol from <35 mg/dL to <40 mg/dL because the latter is a better measure of a depressed HDL
• Lowers the triglyceride classification cutpoints to give more attention to moderate elevations
Support for Implementation
• Recommends a complete lipoprotein profile (total, LDL, and HDL cholesterol and triglycerides) as the preferred initial test, rather than screening for total cholesterol and HDL alone
• Encourages use of plant stanols/sterols and viscous (soluble) fiber as therapeutic dietary options to enhance lowering of LDL cholesterol
• Presents strategies for promoting adherence to therapeutic lifestyle changes and drug therapies
• Recommends treatment beyond LDL lowering for persons with triglycerides ≥200 mg/dL

*ATP indicates Adult Treatment Panel; CHD, coronary heart disease; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

Table 2. ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)*

LDL cholesterol	
<100	Optimal
100-129	Near or above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL cholesterol	
<40	Low
≥60	High

*ATP indicates Adult Treatment Panel; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

Table 3. Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals*

- Cigarette smoking
- Hypertension (blood pressure ≥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; CHD in female first-degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)

*Diabetes is regarded as a coronary heart disease (CHD) risk equivalent. LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

†HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes 1 risk factor from the total count.

Table 4. Three Categories of Risk That Modify LDL Cholesterol Goals

Risk Category	LDL Goal (mg/dL)
CHD and CHD risk equivalents	<100
Multiple (2+) risk factors*	<130
0-1 risk factor	<160

*Risk factors that modify the low-density lipoprotein (LDL) goal are listed in Table 3. CHD indicates coronary heart disease.

Method of Risk Assessment: Counting Major Risk Factors and Estimating 10-Year CHD Risk

Risk status in persons without clinically manifest CHD or other clinical forms of atherosclerotic disease is determined by a 2-step procedure. First, the number of risk factors is counted (Table 3). Second, for persons with multiple (2+) risk factors, 10-year risk assessment is carried out with Framingham scoring (see Appendix) to identify individuals whose short-term (10-

year) risk warrants consideration of intensive treatment. Estimation of the 10-year CHD risk adds a step to risk assessment beyond risk factor counting, but this step is warranted because it allows better targeting of intensive treatment to people who will benefit from it. When 0-1 risk factor is present, Framingham scoring is not necessary because 10-year risk rarely reaches levels for intensive intervention; a very high LDL level in such a person may nevertheless warrant consideration of drug therapy to reduce long-term risk. Risk factors used in Framingham scoring include age, total cholesterol, HDL cholesterol, blood pressure, and cigarette smoking. Total cholesterol is used for 10-year risk assessment because of a larger and more robust Framingham database for total than for LDL cholesterol, but LDL cholesterol is the primary target of therapy. Framingham scoring divides persons with multiple risk factors into those with 10-year risk for CHD of >20%, 10%-20%, and <10%. It should be noted that this 2-step sequence can be reversed with essentially the same results. (If Framingham scoring is carried out before risk factor counting, persons with <10% risk are then divided into those with 2+ risk factors and 0-1 risk factor by risk factor counting to determine the appropriate LDL goal [Table 4].) Initial risk assessment in ATP III uses the major risk factors to define the core risk status. Only after the core risk status has been determined should any other risk modifiers be taken into consideration for adjusting the therapeutic approach.

Role of Other Risk Factors in Risk Assessment

ATP III recognizes that risk for CHD is influenced by other factors not included among the major, independent risk factors (Table 3). Among these are life-habit risk factors and emerging risk factors. The former include obesity, physical inactivity, and atherogenic diet; the latter consist of lipoprotein(a), homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease. The life-habit risk factors are direct targets for clinical intervention but are not used to set a lower LDL cholesterol goal of therapy. The emerging risk factors do not categorically modify LDL cholesterol goals; however, they appear to contribute to CHD risk to varying degrees and can have utility in selected persons to guide intensity of risk-reduction therapy. Their presence can modulate clinical judgment when making therapeutic decisions.

Metabolic Syndrome

Many persons have a constellation of major risk factors, life-habit risk factors, and emerging risk factors that constitute a condition called the metabolic syndrome. Factors characteristic of the metabolic syndrome are abdominal obesity, atherogenic dyslipidemia (elevated triglyceride, small LDL particles, low HDL cholesterol), raised blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states. ATP III recognizes the metabolic syndrome as a secondary target of risk-reduction therapy, after the primary target—LDL cholesterol. Diagnosis and treatment of the metabolic syndrome is described below under "Benefit Beyond LDL Lowering: The Metabolic Syndrome as a Secondary Target of Therapy."

The Link Between Risk Assessment and Cost-effectiveness

In ATP III, a primary aim is to match intensity of LDL-lowering therapy with absolute risk. Everyone with elevated LDL cholesterol is treated with lifestyle changes that are effective in lowering LDL levels. Persons at relatively high risk are also candidates for drug treatment, which is very effective but entails significant additional expense. The cutpoints for drug treatment are based primarily on risk-benefit considerations: those at higher risk are likely to get greater benefit. However, cutpoints for recommended management based on therapeutic efficacy are checked against currently accepted standards for cost-effectiveness. Lifestyle changes are the most cost-effective means to reduce risk for CHD. Even so, to achieve maximal benefit, many persons will require LDL-lowering drugs. Drug therapy is the major expense of LDL-lowering therapy and it dominates cost-effectiveness analysis. However, the costs of LDL-lowering drugs are currently in flux and appear to be declining. This report recognizes that as drug prices decline it will be possible to extend drug use to lower-risk persons and still be cost-effective. In addition, ATP III recognizes that some persons with high long-term risk are candidates for LDL-lowering drugs even though use of drugs may not be cost-effective by current standards.

PRIMARY PREVENTION WITH LDL-LOWERING THERAPY

Primary prevention of CHD offers the greatest opportunity for reducing the burden of CHD in the United States. The clinical approach to primary prevention is founded on the public health approach that calls for lifestyle changes, including (1) reduced intakes of saturated fat and cholesterol, (2) increased physical activity, and (3) weight control, to lower population cholesterol levels and reduce CHD risk, but the clinical approach intensifies preventive strategies for higher-risk persons. One aim of primary prevention is to reduce long-term risk (>10 years) as well as short-term risk (≤10 years). LDL goals in primary prevention depend on a person's absolute risk for CHD (ie, the probability of having a CHD event in the short term or the long term)—the higher the risk, the lower the goal. Therapeutic lifestyle changes are the foundation of clinical primary prevention. Nonetheless, some persons at higher risk because of high or very high LDL cholesterol levels or because of multiple risk factors are candidates for LDL-lowering drugs. Recent primary prevention trials show that LDL-lowering drugs reduce risk for major

coronary events and coronary death even in the short term.

Any person with elevated LDL cholesterol or other form of hyperlipidemia should undergo clinical or laboratory assessment to rule out secondary dyslipidemia before initiation of lipid-lowering therapy. Causes of secondary dyslipidemia include:

- Diabetes
- Hypothyroidism
- Obstructive liver disease
- Chronic renal failure
- Drugs that increase LDL cholesterol and decrease HDL cholesterol (progestins, anabolic steroids, and corticosteroids).

Once secondary causes have been excluded or, if appropriate, treated, the goals for LDL-lowering therapy in primary prevention are established according to a person's risk category (Table 4).

SECONDARY PREVENTION WITH LDL-LOWERING THERAPY

Recent clinical trials demonstrate that LDL-lowering therapy reduces total mortality, coronary mortality, major coronary events, coronary artery procedures, and stroke in persons with established CHD. As shown in Table 2, an LDL cholesterol level of <100 mg/dL is optimal; therefore, ATP III specifies an LDL cholesterol level of <100 mg/dL as the goal of therapy in secondary prevention. This goal is supported by clinical trials with both clinical and angiographic end points and by prospective epidemiological studies. The same goal should apply for persons with CHD risk equivalents. When persons are hospitalized for acute coronary syndromes or coronary procedures, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge. Adjustment of therapy may be needed after 12 weeks.

LDL-LOWERING THERAPY IN 3 RISK CATEGORIES

The 2 major modalities of LDL-lowering therapy are therapeutic lifestyle changes (TLC) and drug therapy. Both are described in more detail later. The TLC Diet stresses reductions in saturated fat and cholesterol intakes. When the metabolic syndrome or its associated lipid risk factors (elevated triglyceride or low HDL cholesterol) are present, TLC also stresses weight reduction and increased physical activity. **TABLE 5** defines LDL cholesterol goals and cutpoints for initiation of TLC and for drug consideration for persons with 3 categories of risk: CHD and CHD risk equivalents; multiple (2+) risk factors (10-year risk 10%-20% and <10%); and 0-1 risk factor.

CHD and CHD Risk Equivalents

For persons with CHD and CHD risk equivalents, LDL-lowering therapy greatly reduces risk for major coronary events and stroke and yields highly favorable cost-effectiveness ratios. The cutpoints for initiating lifestyle and drug therapies are shown in Table 5.

If baseline LDL cholesterol is ≥130 mg/dL, intensive lifestyle therapy and maximal control of other risk factors should be started. Moreover, for most patients, an LDL-lowering drug will be required to achieve an LDL cholesterol level of <100 mg/dL; thus an LDL-cholesterol lowering drug can be started simultaneously with TLC to attain the goal of therapy.

If LDL cholesterol levels are 100-129 mg/dL, either at baseline or on LDL-lowering therapy, several therapeutic approaches are available:

- Initiate or intensify lifestyle and/or drug therapies specifically to lower LDL.
- Emphasize weight reduction and increased physical activity in persons with the metabolic syndrome.
- Delay use or intensification of LDL-lowering therapies and institute treatment of other lipid or nonlipid risk factors; consider use of other lipid-modifying drugs (eg, nicotinic acid or fibric acid) if the patient has elevated triglyceride or low HDL cholesterol.

If baseline LDL cholesterol is <100 mg/dL, further LDL-lowering therapy is not required. Patients should nonetheless be advised to follow the TLC Diet on their own to help keep the LDL level optimal. Several clinical trials are currently under way to assess benefit of lowering LDL cholesterol to well below 100 mg/dL. At present, emphasis should be placed on controlling other lipid and nonlipid risk factors and on treatment of the metabolic syndrome, if present.

Multiple (2+) Risk Factors and 10-Year Risk of ≤20%

For persons with multiple (2+) risk factors and 10-year risk ≤20%, intensity of therapy is adjusted according to 10-year risk and LDL cholesterol level. The treatment approach for each category is summarized in Table 5.

Multiple (2+) Risk Factors and a 10-Year Risk of 10%-20%. In this category, the goal for LDL cholesterol is <130 mg/dL. The therapeutic aim is to reduce short-term risk as well as long-term risk for CHD. If baseline LDL cholesterol is ≥130 mg/dL, TLC is initiated and maintained for 3 months. If LDL remains ≥130 mg/dL after 3 months of TLC, consideration can be given to starting an LDL-lowering drug to achieve the LDL goal of <130 mg/dL. Use of LDL-lowering drugs at this risk level reduces CHD risk and is cost-effective. If the LDL falls to less than 130 mg/dL on TLC alone, TLC can be continued without adding drugs. In older persons (≥65 years), clinical judgment is required for how intensively to apply these guidelines; a variety of factors, including concomitant illnesses, general health status, and social issues, may influence treatment decisions and may suggest a more conservative approach.

Multiple (2+) Risk Factors and a 10-Year Risk of <10%. In this category, the goal for LDL cholesterol also is <130 mg/dL. The therapeutic aim, however, is primarily to reduce longer-term risk. If baseline LDL cholesterol is ≥130 mg/dL, the TLC Diet is initiated to reduce LDL cholesterol. If LDL

Table 5. LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) 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)

*LDL indicates low-density lipoprotein; CHD, coronary heart disease.
†Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, eg, 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.

Table 6. Nutrient Composition of the Therapeutic Lifestyle Changes (TLC) Diet

Nutrient	Recommended Intake
Saturated fat*	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25%-35% of total calories
Carbohydrate†	50%-60% of total calories
Fiber	20-30 g/d
Protein	Approximately 15% of total calories
Cholesterol	<200 mg/d
Total calories‡	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

*Trans fatty acids are another LDL-raising fat that should be kept at a low intake.
†Carbohydrates should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.
‡Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 kcal/d).

is <160 mg/dL on TLC alone, it should be continued. LDL-lowering drugs generally are not recommended because the patient is not at high short-term risk. On the other hand, if LDL cholesterol is ≥160 mg/dL, drug therapy can be considered to achieve an LDL cholesterol level of <130 mg/dL; the primary aim is to reduce long-term risk. Cost-effectiveness is marginal, but drug therapy can be justified to slow development of coronary atherosclerosis and to reduce long-term risk for CHD.

0-1 Risk Factor

Most persons with 0-1 risk factor have a 10-year risk <10%. They are managed according to Table 5. The goal for LDL cholesterol in this risk category is <160 mg/dL. The primary aim of therapy is to reduce long-term risk. First-line therapy is TLC. If after 3 months of TLC the LDL cholesterol is <160 mg/dL, TLC is continued. However, if LDL cholesterol is 160-189 mg/dL after an adequate trial of TLC, drug therapy is optional depending on clinical judgment. Factors favoring use of drugs include:

- A severe single risk factor (heavy cigarette smoking, poorly controlled hypertension, strong family history of premature CHD, or very low HDL cholesterol)
- Multiple life-habit risk factors and emerging risk factors (if measured)
- 10-year risk approaching 10% (if measured; see Appendix). If LDL cholesterol is ≥190 mg/dL despite TLC, drug therapy should be considered to achieve the LDL goal of <160 mg/dL.

The purpose of using LDL-lowering drugs in persons with 0-1 risk factor and elevated LDL cholesterol (≥160 mg/dL) is to slow the development of coronary atherosclerosis, which will reduce long-term risk. This aim may conflict with cost-effectiveness considerations; thus, clinical judgment is required in selection of persons for drug therapy, although a strong case can be made for using drugs when LDL cholesterol is ≥190 mg/dL after TLC.

For persons whose LDL cholesterol levels are already below goal levels upon first encounter, instructions for appropriate changes in life habits, periodic follow-up, and control of other risk factors are needed.

THERAPEUTIC LIFESTYLE CHANGES IN LDL-LOWERING THERAPY

ATP III recommends a multifaceted lifestyle approach to reduce risk for CHD. This approach is designated therapeutic lifestyle changes (TLC). Its essential features are:

- Reduced intakes of saturated fats (<7% of total calories) and cholesterol (<200 mg/d) (see **TABLE 6** for overall composition of the TLC Diet)
- Therapeutic options for enhancing LDL lowering such as plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10-25 g/d)
- Weight reduction
- Increased physical activity.

A model of steps in TLC is shown in **FIGURE 1**. To initiate TLC, intakes of saturated fats and cholesterol are reduced first to lower LDL cholesterol. To improve overall health, ATP III's TLC Diet generally contains the recommendations embodied in the Dietary Guidelines for Americans 2000. One exception is that total fat is allowed to range from 25%-35% of total calories provided saturated fats and *trans* fatty acids are kept low. A higher intake of total fat, mostly in the form of unsaturated fat, can help to reduce triglycerides and raise HDL cholesterol in persons with the metabolic syndrome. In accord with the Dietary Guidelines, moderate physical activity is encouraged. After 6 weeks, the LDL response is determined; if the LDL cholesterol goal has not been achieved, other therapeutic options for LDL lowering such as plant stanol/sterols and viscous fiber can be added.

After maximum reduction of LDL cholesterol with dietary therapy, emphasis shifts to management of the

metabolic syndrome and associated lipid risk factors. The majority of persons with these latter abnormalities are overweight or obese and sedentary. Weight reduction therapy for overweight or obese patients will enhance LDL lowering and will provide other health benefits including modifying other lipid and nonlipid risk factors. Assistance in the management of overweight and obese persons is provided by the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* from the NHLBI Obesity Education Initiative (1998). Additional risk reduction can be achieved by simultaneously increasing physical activity.

At all stages of dietary therapy, physicians are encouraged to refer patients to registered dietitians or other qualified nutritionists for *medical nutrition therapy*, which is the term for the nutritional intervention and guidance provided by a nutrition professional.

DRUG THERAPY TO ACHIEVE LDL CHOLESTEROL GOALS

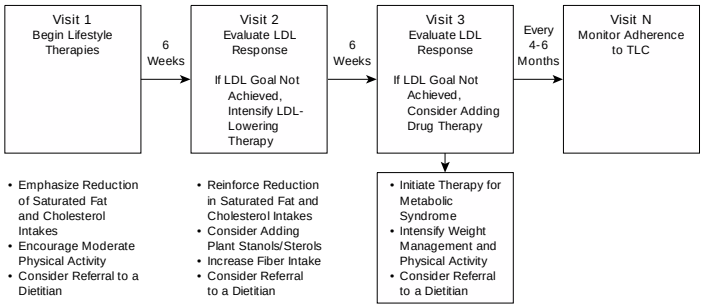
A portion of the population whose short-term or long-term risk for CHD is high will require LDL-lowering drugs in addition to TLC to reach the designated goal for LDL cholesterol (see Table 5). When drugs are prescribed, attention to TLC should always be maintained and reinforced. Currently available drugs that affect lipoprotein metabolism and their major characteristics are listed in **TABLE 7**.

Some cholesterol-lowering agents are currently available over-the-counter (OTC) (eg, nicotinic acid), and manufacturers of several classes of LDL-lowering drugs (eg, statins, bile acid sequestrants) have applied to the Food and Drug Administration (FDA) to allow these agents to become OTC medications. At the time of publication of ATP III, the FDA has not granted permission for OTC status for statins or bile acid sequestrants. If an OTC cholesterol-lowering drug is or becomes available, patients should continue to consult with their physicians about whether to initiate drug treatment, about setting the goals of therapy, and about monitoring for therapeutic responses and side effects.

Secondary Prevention: Drug Therapy for CHD and CHD Risk Equivalents

For persons with CHD and CHD risk equivalents, the goal is to attain an LDL cholesterol level of <100 mg/dL. The cutpoints for initiating lifestyle and drug

Figure 1. Model of Steps in Therapeutic Lifestyle Changes (TLC)



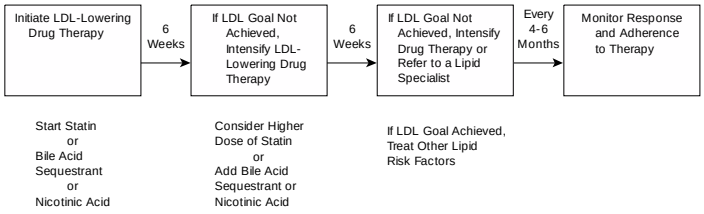
LDL indicates low-density lipoprotein.

Table 7. Drugs Affecting Lipoprotein Metabolism*

Drug Class, Agents, and Daily Doses	Lipid/Lipoprotein Effects	Side Effects	Contraindications	Clinical Trial Results
HMG-CoA reductase inhibitors (statins)†	LDL ↓ 18%-55% HDL ↑ 5%-15% TG ↓ 7%-30%	Myopathy; increased liver enzymes	Absolute: active or chronic liver disease Relative: concomitant use of certain drugs§	Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality
Bile acid sequestrants‡	LDL ↓ 15%-30% HDL ↑ 3%-5% TG No change or increase	Gastrointestinal distress; constipation; decreased absorption of other drugs	Absolute: dysbetalipoproteinemia; TG >400 mg/dL Relative:TG >200 mg/dL	Reduced major coronary events and CHD deaths
Nicotinic acid‖	LDL ↓ 5%-25% HDL ↑ 15%-35% TG ↓ 20%-50%	Flushing; hyperglycemia; hyperuricemia (or gout); upper gastrointestinal distress; hepatotoxicity	Absolute: chronic liver disease; severe gout Relative: diabetes; hyperuricemia; peptic ulcer disease	Reduced major coronary events, and possibly total mortality
Fibric acids¶	LDL ↓ 5%-20% (may be increased in patients with high TG) HDL ↑ 10%-20% TG ↓ 20%-50%	Dyspepsia; gallstones; myopathy; unexplained non-CHD deaths in WHO study	Absolute: severe renal disease; severe hepatic disease	Reduced major coronary events

*HMG-CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; ↓, decrease; ↑, increase; and CHD, coronary heart disease.
†Lovastatin (20-80 mg), pravastatin (20-40 mg), simvastatin (20-80 mg), fluvastatin (20-80 mg), atorvastatin (10-80 mg), and cerivastatin (0.4-0.8 mg).
‡Cholestyramine (4-16 g), colestipol (5-20 g), and colesevelam (2.6-3.8 g).
§Cyclosporine, macrolide antibiotics, various antifungal agents, and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).
‖Immediate-release (crystalline) nicotinic acid (1.5-3 g), extended-release nicotinic acid (1-2 g), and sustained-release nicotinic acid (1-2 g).
¶Gemfibrozil (600 mg twice daily), fenofibrate (200 mg), and clofibrate (1000 mg twice daily).

Figure 2. Progression of Drug Therapy in Primary Prevention



LDL indicates low-density lipoprotein.

therapies are shown in Table 5. Most patients with CHD will need LDL-lowering drug therapy. Other lipid risk factors may also warrant consideration of drug treatment. Whether or not lipid-modifying drugs are used, nonlipid risk factors require attention and favorable modification.

In patients admitted to the hospital for a major coronary event, LDL cholesterol should be measured on admission or within 24 hours. This value can be used for treatment decisions. In general, persons hospitalized for a coronary event or procedure should be discharged on drug therapy if the LDL cholesterol is ≥130 mg/dL. If the LDL is 100-129 mg/dL, clinical judgment should be used in deciding whether to initiate drug treatment at discharge, recognizing that LDL cholesterol levels begin to decline in the first few hours after an event and are significantly decreased by 24 to 48 hours and may remain low for many weeks. Thus, the initial LDL cholesterol level obtained in the hospital may be substantially lower than is usual for the patient. Some authorities hold that drug therapy should be initiated whenever a patient hospitalized for a CHD-related illness is found to have an LDL cholesterol >100 mg/dL. Initiation of drug therapy at the time of hospital discharge has 2 advantages. First, at that time patients are particularly motivated to undertake and adhere to risk-lowering interventions; and second, failure to initiate indicated therapy early is one of the causes of a large "treatment gap," because outpatient follow-up is often less consistent and more fragmented.

LDL-Lowering Drug Therapy for Primary Prevention

Table 5 shows the cutpoints for considering drug treatment in primary prevention. The general approach to management of drug therapy for primary prevention is outlined in **FIGURE 2**.

When drug therapy for primary prevention is a consideration, the third visit of dietary therapy (see Figure 1) will typically be the visit to initiate drug treatment. Even if drug treatment is started, TLC should be continued. As with TLC, the first priority of drug therapy is to achieve the goal for LDL cholesterol. For this reason, an LDL-lowering drug should be started. The usual drug will be a statin, but alternatives are a bile acid sequestrant or nicotinic acid. In most cases, the statin should be started at a moderate dose. In many patients, the LDL cholesterol goal will be achieved, and higher doses will not be necessary. The patient's response should be evaluated about 6 weeks after starting drug therapy. If the goal of therapy has been achieved, the current dose can be maintained. However, if the goal has not been achieved, LDL-lowering therapy can be intensified, either by increasing the dose of statin or by combining a statin with a bile acid sequestrant or nicotinic acid.

After 12 weeks of drug therapy, the response to therapy should again be assessed. If the LDL cholesterol goal is still not achieved, consideration can be given to further intensification of drug therapy. If the LDL goal cannot be attained by standard lipid-lowering therapy, consideration should be given to seeking consultation from a lipid specialist. Once the goal for LDL cholesterol has been attained, attention can turn to other lipid risk factors and nonlipid factors. Thereafter, patients can be monitored for response to therapy every 4 to 6 months, or more often if considered necessary.

BENEFIT BEYOND LDL LOWERING: THE METABOLIC SYNDROME AS A SECONDARY TARGET OF THERAPY

Evidence is accumulating that risk for CHD can be reduced beyond LDL-lowering therapy by modification of other risk factors. One potential secondary target of therapy is the metabolic syndrome, which represents a constellation of lipid and nonlipid risk factors of metabolic origin. This syndrome is closely linked to a generalized metabolic disorder called *insulin resistance* in which the normal actions of insulin are impaired. Excess body fat (particularly abdominal obesity) and physical inactivity promote the development of insulin resistance, but some individuals also are genetically predisposed to insulin resistance.

The risk factors of the metabolic syndrome are highly concordant; in aggregate they enhance risk for CHD at any given LDL cholesterol level. For purposes of ATP III, the diagnosis of the metabolic syndrome is made when 3 or more of the risk determinants shown in **TABLE 8** are present. These determinants include a combination of categorical and borderline risk factors that can be readily measured in clinical practice.

Management of the metabolic syndrome has a 2-fold objective: (1) to reduce underlying causes (ie, obesity and physical inactivity) and (2) to treat associated nonlipid and lipid risk factors.

Management of Underlying Causes of the Metabolic Syndrome

First-line therapies for all lipid and nonlipid risk factors associated with the metabolic syndrome are weight reduction and increased physical activity,

which will effectively reduce all of these risk factors. Therefore, after appropriate control of LDL cholesterol, TLC should stress weight reduction and physical activity if the metabolic syndrome is present.

Weight Control. In ATP III overweight and obesity are recognized as major, underlying risk factors for CHD and identified as direct targets of intervention. Weight reduction will enhance LDL lowering and reduce all of the risk factors of the metabolic syndrome. The recommended approaches for reducing overweight and obesity are contained in the clinical guidelines of the Obesity Education Initiative.

Physical Activity. Physical inactivity is likewise a major, underlying risk factor for CHD. It augments the lipid and nonlipid risk factors of the metabolic syndrome. It further may enhance risk by impairing cardiovascular fitness and coronary blood flow. Regular physical activity reduces very low-density lipoprotein (VLDL) levels, raises HDL cholesterol, and in some persons, lowers LDL levels. It also can lower blood pressure, reduce insulin resistance, and favorably influence cardiovascular function. Thus, ATP III recommends that regular physical activity become a routine component in management of high serum cholesterol. The evidence base for this recommendation is contained in the US Surgeon General's Report on Physical Activity.

Specific Treatment of Lipid and Nonlipid Risk Factors

Beyond the underlying risk factors, therapies directed against the lipid and nonlipid risk factors of the metabolic syndrome will reduce CHD risk. These include treatment of hypertension, use of aspirin in patients with CHD to reduce the prothrombotic state (guidelines for aspirin use in primary prevention have not been firmly established), and treatment of elevated triglycerides and low HDL cholesterol as discussed below under "Management of Specific Dyslipidemias."

SPECIAL ISSUES

Management of Specific Dyslipidemias

Very High LDL Cholesterol (≥190 mg/dL). Persons with very high LDL cholesterol usually have genetic forms of hypercholesterolemia: monogenic familial hypercholesterolemia, familial defective apolipoprotein B, and polygenic hypercholesterolemia. Early detection of these disorders through cholesterol testing in young adults is needed to prevent premature CHD. Family testing is important to identify similarly affected relatives. These disorders often require combined drug therapy (statin + bile acid sequestrant) to achieve the goals of LDL-lowering therapy.

Elevated Serum Triglycerides. Recent meta-analyses of prospective studies indicate that elevated triglycerides are also an independent risk factor for CHD. Factors contributing to elevated (higher than normal) triglycerides in the general population include obesity and overweight, physical inactivity, cigarette smoking, excess alcohol intake, high-carbohydrate diets (>60% of energy intake), several diseases (eg, type 2 diabetes, chronic renal failure, nephrotic syndrome), certain drugs (eg, corticosteroids, estrogens, retinoids, higher doses of β-adrenergic blocking agents), and genetic disorders (familial combined hyperlipidemia, familial hypertriglyceridemia, and familial dysbetalipoproteinemia).

In clinical practice, elevated serum triglycerides are most often observed in persons with the metabolic syndrome, although secondary or genetic factors can heighten triglyceride levels. ATP III adopts the following classification of serum triglycerides:

- Normal triglycerides: <150 mg/dL
- Borderline-high triglycerides: 150-199 mg/dL
- High triglycerides: 200-499 mg/dL
- Very high triglycerides: ≥500 mg/dL

(To convert triglyceride values to mmol/L, divide by 88.6.)

The finding that elevated triglycerides are an independent CHD risk factor suggests that some triglyceride-rich lipoproteins are atherogenic. The latter are partially degraded VLDL, commonly called *remnant lipoproteins*. In clinical practice, VLDL cholesterol is the most readily available measure of atherogenic remnant lipoproteins. Thus, VLDL cholesterol can be a target of cholesterol-lowering therapy. ATP III identifies the sum of LDL + VLDL cholesterol (termed *non-HDL cholesterol* [total cholesterol − HDL cholesterol]) as a secondary target of therapy in persons with high triglycerides (≥200 mg/dL). The goal for non-HDL cholesterol in persons with high serum triglycerides can be set at 30 mg/dL higher than that for LDL cholesterol (**TABLE 9**) on the premise that a VLDL cholesterol level ≤30 mg/dL is normal.

The treatment strategy for elevated triglycerides depends on the causes of the elevation and its severity. For all persons

Table 8. Clinical Identification of the Metabolic Syndrome

Risk Factor	Defining Level
• Abdominal obesity* (waist circumference)†	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
• Triglycerides	≥150 mg/dL
• High-density lipoprotein cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
• Blood pressure	≥130/≥85 mm Hg
• Fasting glucose	≥110 mg/dL

*Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

†Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, eg, 94-102 cm (37-40 in). Such patients may have strong genetic contribution to insulin resistance and they should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

Table 9. Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for 3 Risk Categories*

Risk Category	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
CHD and CHD risk equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) risk factors and 10-year risk ≤20%	<130	<160
0-1 Risk factor	<160	<190

*LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; and CHD, coronary heart disease.

with borderline high or high triglycerides, the primary aim of therapy is to achieve the target goal for LDL cholesterol. When triglycerides are borderline high (150-199 mg/dL), emphasis should also be placed on weight reduction and increased physical activity. For high triglycerides (200-499 mg/dL), non-HDL cholesterol becomes a secondary target of therapy. Aside from weight reduction and increased physical activity, drug therapy can be considered in high-risk persons to achieve the non-HDL cholesterol goal. There are 2 approaches to drug therapy. First, the non-HDL cholesterol goal can be achieved by intensifying therapy with an LDL-lowering drug; second, nicotinic acid or fibrate can be added, if used with appropriate caution, to achieve the non-HDL cholesterol goal by further lowering VLDL cholesterol. In rare cases in which triglycerides are very high (≥500 mg/dL), the initial aim of therapy is to prevent acute pancreatitis through triglyceride lowering. This approach requires very low-fat diets (≤15% of calorie intake), weight reduction, increased physical activity, and usually a triglyceride-lowering drug (fibrate or nicotinic acid). Only after triglyceride levels have been lowered to <500 mg/dL should attention turn to LDL lowering to reduce risk for CHD.

Low HDL Cholesterol. Low HDL cholesterol is a strong independent predictor of CHD. In ATP III, low HDL cholesterol is defined categorically as a level <40 mg/dL, a change from the level of <35 mg/dL in ATP II. In the present guidelines, low HDL cholesterol both modifies the goal for LDL-lowering therapy and is used as a risk factor to estimate 10-year risk for CHD.

Low HDL cholesterol levels have several causes, many of which are associated with insulin resistance, ie, elevated triglycerides, overweight and obesity, physical inactivity, and type 2 diabetes. Other causes are cigarette smoking, very high carbohydrate intakes (>60% of calories), and certain drugs (eg, β-blockers, anabolic steroids, progestational agents).

ATP III does not specify a goal for HDL raising. Although clinical trial results suggest that raising HDL will reduce risk, the evidence is insufficient to specify a goal of therapy. Furthermore, currently available drugs do not robustly raise HDL cholesterol. Nonetheless, a low HDL should receive clinical attention and management according to the following sequence. In all persons with low HDL cholesterol, the primary target of therapy is LDL cholesterol; ATP III guidelines should be followed to achieve the LDL cholesterol goal. Second, after the LDL goal has been reached, emphasis shifts to weight reduction and increased physical activity (when the metabolic syndrome is present). When a low HDL cholesterol is associated with high triglycerides (200-499 mg/dL), secondary priority goes to achieving the non-HDL cholesterol goal, as outlined earlier. Also, if triglycerides are <200 mg/dL (isolated low HDL cholesterol), drugs for HDL raising (fibrates or nicotinic acid) can be considered; however, treatment for isolated low HDL is mostly reserved for persons with CHD and CHD risk equivalents.

Diabetic Dyslipidemia. This disorder is essentially atherogenic dyslipidemia in persons with type 2 diabetes. Although elevated triglycerides, low HDL cholesterol, or both are common in persons with diabetes, clinical trial results support the identification of LDL cholesterol as the primary target of therapy, as it is in those without diabetes. Since diabetes is designated a CHD risk equivalent in ATP III, the LDL cholesterol goal of therapy for most persons with diabetes will be <100 mg/dL. Furthermore, when LDL cholesterol is ≥130 mg/dL, most persons with diabetes will require initiation of LDL-lowering drugs simultaneously with TLC to achieve the LDL goal. When LDL cholesterol levels are in the range of 100-129 mg/dL at baseline or on treatment, several therapeutic options are available: increasing intensity of LDL-lowering therapy, adding a drug to modify atherogenic dyslipidemia (fibrate or nicotinic acid), or intensifying control of other risk factors including hyperglycemia. When triglyceride levels are ≥200 mg/dL, non-HDL cholesterol becomes a secondary target of cholesterol-lowering therapy. Several ongoing clinical trials (eg, Antihypertensive and Lipid Lowering Heart Attack Trial [ALLHAT]) will better quantify the magnitude of the benefit of LDL-lowering treatment in older individuals with diabetes. In older persons (≥65 years) with diabetes but no additional CHD risk factors other than age, clinical judgment is required for how intensively to apply these guidelines. A variety of factors, including concomitant illnesses, general health status, and social issues, may influence treatment decisions and may suggest a more conservative approach.

Special Considerations for Different Population Groups

Middle-Aged Men (35-65 Years). In general, men have a higher risk for CHD than do women. Middle-aged men in particular have a high prevalence of the major risk factors and are predisposed to abdominal obesity and the metabolic syndrome. A sizable fraction of all CHD in men occurs in middle age. Thus, many middle-aged men carry a relatively high risk for CHD, and for those who do, intensive LDL-lowering therapy is needed.

Women Aged 45-75 Years. In women, onset of CHD generally is delayed by some 10 to 15 years compared with that in men; thus, most CHD in women occurs after age 65 years. All risk factors contribute to CHD in women, and most premature CHD in women (<65 years) occurs in those with multiple risk factors and the metabolic syndrome. Despite the previous belief that the sex difference in risk for CHD reflects a protective effect of estrogen in women, recent secondary and primary prevention trials cast doubt on the use of hormone replacement therapy to reduce CHD risk in postmenopausal women. In contrast, the favorable effects of statin therapy in women in clinical trials make a cholesterol-lowering drug preferable to hormone replacement therapy for CHD risk reduction. Women should be treated similarly to men for secondary prevention. For primary prevention, ATP III's general approach is similarly applicable for women and men. However, the later on-

Table 10. Interventions to Improve Adherence

Focus on the Patient
• Simplify medication regimens
• Provide explicit patient instruction and use good counseling techniques to teach the patient how to follow the prescribed treatment
• Encourage the use of prompts to help patients remember treatment regimens
• Use systems to reinforce adherence and maintain contact with the patient
• Encourage the support of family and friends
• Reinforce and reward adherence
• Increase visits for patients unable to achieve treatment goal
• Increase the convenience and access to care
• Involve patients in their care through self-monitoring
Focus on the Physician and Medical Office
• Teach physicians to implement lipid treatment guidelines
• Use reminders to prompt physicians to attend to lipid management
• Identify a patient advocate in the office to help deliver or prompt care
• Use patients to prompt preventive care
• Develop a standardized treatment plan to structure care
• Use feedback from past performance to foster change in future care
• Remind patients of appointments and follow up missed appointments
Focus on the Health Delivery System
• Provide lipid management through a lipid clinic
• Utilize case management by nurses
• Deploy telemedicine
• Utilize the collaborative care of pharmacists
• Execute critical care pathways in hospitals

set of CHD for women in general should be factored into clinical decisions about use of cholesterol-lowering drugs.

Older Adults (Men ≥65 Years and Women ≥75 Years). Overall, most new CHD events and most coronary deaths occur in older persons (≥65 years). A high level of LDL cholesterol and low HDL cholesterol still carry predictive power for the development of CHD in older persons. Nevertheless, the finding of advanced subclinical atherosclerosis by noninvasive testing can be helpful for confirming the presence of high risk in older persons. Secondary prevention trials with statins have included a sizable number of older persons, mostly in the age range of 65 to 75 years. In these trials, older persons showed significant risk reduction with statin therapy. Thus, no hard-and-fast age restrictions appear necessary when selecting persons with established CHD for LDL-lowering therapy. For primary prevention, TLC is the first line of therapy for older persons. However, LDL-lowering drugs can also be considered when older persons are at higher risk because of multiple risk factors or advanced subclinical atherosclerosis.

Younger Adults (Men 20-35 Years; Women 20-45 Years). In this age group, CHD is rare except in those with severe risk factors, eg, familial hypercholesterolemia, heavy cigarette smoking, or diabetes. Even though clinical CHD is relatively rare in young adults, coronary atherosclerosis in its early stages may progress rapidly. The rate of development of coronary atherosclerosis earlier in life correlates with the major risk factors. In particular, long-term prospective studies reveal that elevated serum cholesterol detected in young adulthood predicts a higher rate of premature CHD in middle age. Thus, risk factor identification in young adults is an important aim for long-term prevention. The combination of early detection and early intervention on elevated LDL cholesterol with life-habit changes offers the opportunity for delaying or preventing onset of CHD later in life. For young adults with LDL cholesterol levels of ≥130 mg/dL, TLC should be instituted and emphasized. Particular attention should be given to young men who smoke and have a high LDL cholesterol (160-189 mg/dL); they may be candidates for LDL-lowering drugs. When young adults have very high LDL cholesterol levels (≥190 mg/dL), drug therapy should be considered, as in other adults. Those with severe genetic forms of hypercholesterolemia may require LDL-lowering drugs in combination (eg, statin+bile acid sequestrant).

Racial and Ethnic Groups. African Americans have the highest overall CHD mortality rate and the highest out-of-hospital coronary death rates of any ethnic group in the United States, particularly at younger ages. Although the reasons for the excess CHD mortality among African Americans have not been fully elucidated, it can be accounted for, at least in part, by the high prevalence of coronary risk factors. Hypertension, left ventricular hypertrophy, diabetes mellitus, cigarette smoking, obesity, physical inactivity, and multiple CHD risk factors all occur more frequently in African Americans than in whites. Other ethnic groups and minority populations in the United States include Hispanics, Native Americans, Asian and Pacific Islanders, and South Asians. Although limited data suggest that racial and ethnic groups vary somewhat in baseline risk for CHD, this evidence did not appear sufficient to lead the ATP III panel to modify general recommendations for cholesterol management in these populations.

ADHERENCE TO LDL-LOWERING THERAPY

Adherence to the ATP III guidelines by both patients and providers is a key to approximating the magnitude of the benefits demonstrated in clinical trials of cholesterol lowering. Adherence issues have to be addressed to attain the highest possible levels of CHD risk reduction. Thus, ATP III recommends the use of state-of-the-art multidisciplinary methods targeting the patient, clinicians, and health delivery systems to achieve the full population effectiveness of the guidelines for primary and secondary prevention (**TABLE 10**).

National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Members: Scott M. Grundy, MD, PhD (Chair of the panel), Diane Becker, RN, MPH, ScD, Luther T. Clark, MD, Richard S. Cooper, MD, Margo A. Denke, MD, Wm. James Howard, MD, Donald B. Hunninghake, MD, D. Roger Illingworth, MD, PhD, Russell V. Luepker, MD, MS, Patrick McBride, MD, MPH, James M. McKenney, PharmD, Richard C. Pasternak, MD, Neil J. Stone, MD, Linda Van Horn, PhD, RD

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Executive Committee Liaison to the Panel: Stephen Havas, MD, MPH, MS
Reviewers of the Full Report of ATP III: Eugene Braunwald, MD, W. Virgil Brown, MD, Alan Chait, MD, James E. Dalen, MD, Valentin Fuster, MD, PhD, Henry N. Ginsberg, MD, Antonio M. Gotto, MD, DPhil, Ronald M. Krauss, MD, John C. LaRosa, MD, Thomas H. Lee, Jr, MD, Linda Meyers, PhD, Michael Newman, MD, Thomas Pearson, MD, PhD, Daniel J. Rader, MD, Frank M. Sacks, MD, Ernst J. Schaefer, MD, Sheldon G. Sheps, MD, Lynn A. Smaha, MD, PhD, Sidney C. Smith, Jr, MD, Jeremiah Stamler, MD, Daniel Steinberg, MD, PhD, Nanette K. Wenger, MD
National Cholesterol Education Program Coordinating Committee: The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults was approved by the National Cholesterol Education Program Coordinating Committee, which comprises the following organizational representatives:
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APPENDIX

Shared Features of ATP III and ATP II

Adult Treatment Panel (ATP) III shares a set of core features with ATP II, shown in Table A.

Table A. Shared Features of ATP III and ATP 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 factor, 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 CHD
- Identification of 3 categories of risk for different LDL goals and different intensities of LDL-lowering therapy:
  - CHD and CHD 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

*ATP indicates Adult Treatment Panel; LDL, low-density lipoprotein; and CHD, coronary heart disease.
†A CHD risk equivalent is a condition that carries an absolute risk for developing new CHD equal to the risk for having recurrent CHD events in persons with established CHD.
‡Risk factors that continue to modify the LDL goal include cigarette smoking, hypertension, low HDL cholesterol, family history of premature CHD, age (male ≥45 years and female ≥55 years), and diabetes (in ATP III diabetes is regarded as a CHD risk equivalent).

Estimating 10-Year Risk for Men and Women

Risk assessment for determining the 10-year risk for developing CHD is carried out using Framingham risk scoring (Table B1 for men and Table B2 for women). The risk factors included in the Framingham calculation of 10-year risk are age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking. The first step is to calculate the number of points for each risk factor. For initial assessment, values for total cholesterol and HDL cholesterol are required. Because of a larger database, Framingham estimates are more robust for total cholesterol than for LDL cholesterol. Note, however, that the LDL cholesterol level remains the primary target of therapy. Total cholesterol and HDL cholesterol values should be the average of at least 2 measurements obtained from lipoprotein analysis. The blood pressure value used is that obtained at the time of assessment, regardless of whether the person is on antihypertensive therapy. However, if the person is on antihypertensive treatment, an extra point is added beyond points for the blood pressure reading because treated hypertension carries residual risk (Tables B1 and B2). The average of several blood pressure measurements, as recommended by the Joint National Committee (JNC), is needed for an accurate measure of baseline blood pressure. The designation "smoker" means any cigarette smoking in the past month. The total risk score sums the points for each risk factor. The 10-year risk for myocardial infarction and coronary death (hard CHD) is estimated from total points, and the person is categorized according to absolute 10-year risk as indicated above (see Table 5).

Table B1. Estimate of 10-Year Risk for **Men** (Framingham Point Scores)

Age, y	Points
20-34	−9
35-39	−4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol, mg/dL	Points				
	Age 20-39 y	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39 y	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL, mg/dL	Points
≥60	−1
50-59	0
40-49	1
<40	2

Systolic BP, mm Hg	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk, %
<0	<1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥30

Table B2. Estimate of 10-Year Risk for **Women** (Framingham Point Scores)

Age, y	Points
20-34	−7
35-39	−3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol, mg/dL	Points				
	Age 20-39 y	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20-39 y	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL, mg/dL	Points
≥60	−1
50-59	0
40-49	1
<40	2

Systolic BP, mm Hg	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk, %
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥30

Appendix 6

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AHA GUIDELINE

Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update

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In addition, this report has been endorsed by the American Academy of Physician Assistants; American Association for Clinical Chemistry; American Association of Cardiovascular and Pulmonary Rehabilitation; American College of Chest Physicians; American College of Emergency Physicians; American Diabetes Association; American Geriatrics Society; American Society for Preventive Cardiology; American Society of Echocardiography; American Society of Nuclear Cardiology; Association of Women's Health, Obstetric and Neonatal Nurses; Global Alliance for Women's Health; The Mended Hearts, Inc; National Black Nurses Association; National Black Women's Health Imperative; National Women's Health Resource Center; North American Menopause Society; The Partnership for Gender-Specific Medicine at Columbia University; Preventive Cardiovascular Nurses Association; Society for Vascular Medicine and Biology; Society for Women's Health Research; Society of Geriatric Cardiology; Women in Thoracic Surgery; and WomenHeart: the National Coalition for Women with Heart Disease.

Worldwide, cardiovascular disease (CVD) is the largest single cause of death among women, accounting for one third of all deaths (1). In many countries, including the United States, more women than men die every year of CVD, a fact largely unknown by physicians (2,3). The public health impact of CVD in women is not related solely to the mortality rate, given that advances in science and medicine allow many women to survive heart disease. For example, in the United States, 38.2 million women (34%) are living with CVD, and the population at risk is even larger (2). In China, a country with a population of approximately 1.3 billion, the age-standardized prevalence rates of dyslipidemia and hypertension in women 35 to 74 years of age are 53% and 25%, respectively, which underscores the enormity of CVD as a

†Representation does not imply endorsement by the American College of Physicians.

Please see the online version of this document for data supplements.

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on January 9, 2007. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0401. To purchase additional reprints: Up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 410-528-4121, fax 410-528-4264, or e-mail kelle.ramsay@wolterskluwer.com.

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global health issue and the need for prevention of risk factors in the first place (4). As life expectancy continues to increase and economies become more industrialized, the burden of CVD on women and the global economy will continue to increase (5).

The human toll and economic impact of CVD are difficult to overstate. In the United States alone, $403 billion was estimated to be spent in 2006 on health care or in lost productivity as a result of CVD, compared with $190 billion for cancer and $29 billion for human immunodeficiency virus (HIV) (2). In addition to population-based and macroeconomic interventions, interventions in individual patients are key to reducing the incidence of CVD globally (6). Prevention of CVD is paramount to the health of every woman and every nation. Even modest control could have an enormous impact. It is projected that a reduction in the death rate due to chronic diseases by just 2% over 1 decade would prevent 36 million deaths (6).

Fortunately, most CVD in women is preventable. In 1999, the American Heart Association (AHA) published a scientific statement titled "A Guide to Preventive Cardiology in Women," which was based on a 1997 review of the literature that documented unique aspects of risk factor management and the occurrence of CVD in women (7,8). Over the subsequent decade, many landmark clinical trials in the prevention of CVD altered the practice of medicine. In 2003, a systematic literature search was conducted to develop evidence-based guidelines for the prevention of CVD in women (9). Demand for clinical trial evidence increased in the wake of the Women's Health Initiative's discordant findings with observational studies of hormone therapy (10). Some commonly used preventive interventions lacked clinical trial data for women, and it was unclear whether results of studies conducted in men could be generalized to women. Since the 2003 literature review, numerous clinical trials that have a bearing on CVD prevention in women have been completed (see Appendix). These new research findings must be interpreted in the context of existing data and as-yet missing information so they can be translated appropriately into practice. With few exceptions (eg, the use of aspirin for primary prevention of heart disease), recommendations to prevent CVD in women do not differ from those for men. Healthcare providers should be aware that in some instances, the risk-reducing interventions recommended in these guidelines (eg, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for blood pressure control) are contraindicated in women contemplating pregnancy or in those who are pregnant.

This 2007 update provides the most current clinical recommendations for the prevention of CVD in women ≥20 years of age and is based on a systematic search of the highest-quality science, interpreted by experts in the fields of cardiology, epidemiology, family medicine, gynecology, internal medicine, neurology, nursing, public health, statistics, and surgery. These guidelines cover the primary and secondary prevention of chronic atherosclerotic vascular diseases. More acute management of vascular disease in the periprocedural or immediate posthospital settings and of valvular heart disease is covered in other AHA guidelines. Management of heart failure, atrial fibrillation for stroke prevention, and CVD risk factors during pregnancy is beyond the scope of the present document.

TABLE 1. Classification of CVD Risk in Women

Risk Status	Criteria
High risk	Established coronary heart disease
	Cerebrovascular disease
	Peripheral arterial disease
	Abdominal aortic aneurysm
	End-stage or chronic renal disease
	Diabetes mellitus
	10-Year Framingham global risk >20%*
At risk	≥1 major risk factors for CVD, including:
	Cigarette smoking
	Poor diet
	Physical inactivity
	Obesity, especially central adiposity
	Family history of premature CVD (CVD at <55 years of age in male relative and <65 years of age in female relative)
	Hypertension
	Dyslipidemia
	Evidence of subclinical vascular disease (eg, coronary calcification)
	Metabolic syndrome
	Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise
Optimal risk	Framingham global risk <10% and a healthy lifestyle, with no risk factors

CVD indicates cardiovascular disease.
*Or at high risk on the basis of another population-adapted tool used to assess global risk.

CVD Risk Assessment in Women

The 2004 guidelines emphasized the importance of recognizing the spectrum of CVD and thus classified women as being at high risk, intermediate risk, lower risk, and optimal risk. Classification was based on clinical criteria and/or the Framingham global risk score (11). These criteria are still used to help guide lipid therapy. The 2007 update recommends a scheme for a general approach to the female patient that classifies her as at high risk, at risk, or at optimal risk (Table 1). The rationale for the change includes several factors: (1) The average lifetime risk for CVD in women is very high, approaching 1 in 2, so prevention is important in all women (12,13); (2) most clinical trial data used to formulate the recommendations included either women at high risk because of known CVD or apparently healthy women with a spectrum of risk, which allowed the current scheme to align the guidelines with the evidence; and (3) there has been a growing appreciation of the limitations of risk stratification with the Framingham risk function in diverse populations of women, including the narrow focus on short-term (10-year) risk of myocardial infarction and coronary heart disease

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death, lack of inclusion of family history, overestimation or underestimation of risk in nonwhite populations, and the documentation of subclinical disease among many women who score as being at low risk (14).

The panel believed that a Framingham global risk score >20% could be used to identify a woman at high risk but that a lower score is not sufficient to ensure that an individual woman is at low risk. Even the presence of a single risk factor at 50 years of age is associated with a substantially increased lifetime absolute risk for CVD and shorter duration of survival (13). Women who are at risk of CVD because they have ≥1 risk factor for heart disease, evidence of subclinical disease with or without risk factors, poor exercise capacity, or unhealthy lifestyles may have a broad range of risk for CVD. For example, a woman found to have coronary calcification or increased carotid intimal thickness may be at low absolute risk of CHD on the basis of the Framingham score, but she may actually be at intermediate or high risk of a future CVD event. Healthcare providers should take several factors into consideration, including medical and lifestyle history, Framingham risk score, family history of CVD, and other genetic conditions (eg, familial hypercholesterolemia), as they make decisions about the aggressiveness of preventive therapy. The optimal risk category has been maintained in the present update and emphasizes the importance of optimizing modifiable risk, especially with regard to maintaining a healthy lifestyle, and may reassure some women or motivate others.

The role that novel CVD risk factors (eg, high-sensitivity C-reactive protein) and novel screening technologies (eg, coronary calcium scoring) should play in guiding preventive interventions is not yet defined. Further research is needed on added benefits, risks, and costs associated with such strategies before they can be incorporated into guidelines. Unique opportunities to identify women's risk (eg, during pregnancy) also deserve further exploration. For example, preeclampsia may be an early indicator of CVD risk (15,16). Women with preeclampsia/eclampsia are significantly more likely to develop hypertension and cerebrovascular disease (15,16). In addition, maternal placental syndromes in combination with traditional cardiovascular risk factors, such as prepregnancy hypertension or diabetes mellitus, obesity, dyslipidemia, or metabolic syndrome, may be additive in defining CVD risk in women (16). Future research should evaluate the potential for events or medical contact during unique phases in a woman's lifespan, such as adolescence, pregnancy, and menopause, to identify women at high risk and to determine the effectiveness of preventive interventions during critical time periods.

Several important changes from the 2004 guidelines should be noted. First, the approach to risk stratification of women places greater emphasis on lifetime risk than on short-term absolute risk, defined by the Framingham global score, in part because of the limitations described above. The panel acknowledged that nearly all women are at risk for CVD, which underscores the importance of a heart-healthy lifestyle. Additionally, some women are at high risk of future events because of established CVD and/or multiple risk factors. These women are candidates for more aggressive preventive therapy. Second, more definitive data about menopausal therapy, aspirin therapy, and folic acid therapy have been published in recent years, and the guidelines have been revised accordingly. Of note is that aspirin therapy should be considered for all women for stroke prevention, depending on the balance of risks and benefits. Finally, an algorithm is provided to assist healthcare providers in evaluating CVD risk in women and prioritizing preventive interventions.

Methods

Selection of Expert Panel

The AHA Manuscript Oversight Committee commissioned the update of the guidelines and approved the chair of the expert panel, who was a nonvoting member of the panel. The leadership of each AHA scientific council and interdisciplinary working group was asked to nominate a recognized expert in CVD prevention who had particular knowledge about women. Major professional or government organizations with a mission consistent with CVD prevention were solicited to serve as cosponsors and were each asked to nominate 1 representative with full voting rights to serve on the expert panel. Each panel member completed a conflict-of-interest statement and was asked to abstain from discussion of or voting on any recommendations they deemed to be a potential conflict of interest. Panelists also suggested diverse professional and community organizations to endorse the final document after its approval by the AHA Science Advisory and Coordinating Committee and cosponsoring organizations.

Selection of Topics and Systematic Search

The expert panel reviewed the list of recommendations in the 2004 guidelines and suggested additional topics to be researched to determine whether they warranted discussion or a clinical recommendation. The methods for the systematic search were similar to those for the research conducted in 2003 and described previously (9). The time period for the updated search was January 2003 through June 7, 2006. New topics were searched electronically on 3 databases from their inception (Medline, 1966 through June 7, 2006; CINAHL, 1982 through June 7, 2006; and PsychInfo, 1872 through June 7, 2006).

Briefly, studies were included if they were randomized clinical trials or large prospective cohort studies (>1000 subjects) of CVD risk–reducing interventions, meta-analyses that used a quantitative systematic review process, or surrogate end-point studies with at least 10 cases of major clinical CVD end points reported. The systematic search was conducted by the Duke Center for Clinical Health Policy Research, Durham, NC. Table 2 lists the number of articles included/excluded for each category of recommendation. A total of 5774 articles were initially identified; 828 were included for full-text screening, and 246 met the inclusion criteria and were included in the evidence tables. Some proposed new topics were searched but not included in the guidelines because the expert panel determined the data were insufficient to make clinical recommendations (eg, yoga/stress reduction) or because the topic had been covered in other recent guidelines (eg, treatment of atrial fibrillation for stroke prevention) (17,18). The summary

TABLE 2. Summary of Articles Identified From Systematic Literature Review, by Topic (2006)

Topic	Abstracts Identified	Articles Included for Full-Text Screening	Meta-Analyses Identified	Articles Included for Evidence Tables
Hyperlipidemia	166	27	5	9
Physical activity	298*	53†	1	11
Smoking	281	71	0	1
Antiplatelet therapy	402	95‡	7	12
Hypertension	78	32	1	10
β-Blocker therapy	234	17	1	4
Cardiac rehabilitation	298*	53†	3	3
ACE/ARB therapy	251	44	7	13
Weight management	52	4	0	1
Diabetes mellitus	119	14	2	8
Hormone replacement therapy/SERMs§	154	24	1	10
Diet modification	144	123‡	1	28
Warfarin, antiplatelet therapy,§ and antiarrhythmic therapy§ in atrial fibrillation	460	73	23	27
Aspirin for primary prevention	7	95†	2	1
Psychosocial§/depression	409	42	0	10
Antioxidant supplementation	48	13	3	5
Omega-3 fatty acid supplementation	87	23	3	4
Folic acid supplementation, vitamin B6,§ vitamin B12§	192	36	0	8
New search terms				
Alcohol	325	123‡	0	57
CHF rehabilitation	388	31	4	3
PVD rehabilitation	94	22	0	0
Yoga/stress reduction	83	20	2	6
Aldosterone blocker	239	7	0	4
Stroke rehabilitation	1263	57	11	11
Total	5774	828	77	246

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; SERMs, selective estrogen-receptor modulators; CHF, congestive heart failure; and PVD, peripheral vascular disease.

*Physical activity and cardiac rehabilitation were combined during the initial literature search and full-text screening phase. This number reflects the total number of abstracts identified and articles included at full text as physical activity or cardiac rehabilitation.

†Antiplatelet therapy for coronary artery disease and aspirin for primary prevention were combined during the full-text screening phase. This number reflects the total number of articles included at full text as antiplatelet therapy for coronary artery disease or aspirin for primary prevention.

‡Diet modification and alcohol were combined during the full-text screening phase. This number reflects the total number of articles included at full text as diet modification or alcohol.

§New search term for 2006 combined with previous 2003 topic.

evidence used by the expert panel can be obtained online as a Data Supplement.

Evidence Rating and Recommendation Procedures

A series of conference calls to discuss recommendations was conducted. Primary and secondary reviewers were assigned to each recommendation to modify any wording and to ensure that the evidence tables were complete for that topic. Each expert received a final copy of the evidence tables and voted independently on the strength of the recommendation (Class I, IIa, IIb, or III) and level of evidence (A, B, or C) as outlined in Table 3. The final rating of evidence was determined by a majority vote. Modifications to text and clinical recommendations were made on the basis of peer review comments and cosponsor reviews. The guidelines were then finalized and approved by the expert panel.

Clinical Recommendations and Limitations

Evidence-based recommendations for the prevention of CVD in women are listed in Table 4. Each recommendation is accompanied by the strength of recommendation and the level of evidence to support it. The strength of the recommendation is based not only on the level of evidence to support a clinical recommendation but also on other factors, such as the feasibility of conducting randomized controlled trials in women. Recommendations are grouped in the following categories: lifestyle interventions, major risk factor interventions, and preventive drug interventions. Table 5 lists Class III interventions that are not recommended for the prevention of CVD, or myocardial infarction in particular, on the basis of current evidence.

The expert panel tried to simplify the guidelines as much as possible while attempting to preserve the integrity of the evidence-based process. This required the assumption of a

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TABLE 3. Classification and Levels of Evidence

	Strength of Recommendation
Classification	
Class I	Intervention is useful and effective.
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Intervention is not useful/effective and may be harmful.
Level of evidence	
A	Sufficient evidence from multiple randomized trials
B	Limited evidence from single randomized trial or other nonrandomized studies
C	Based on expert opinion, case studies, or standard of care

class effect for most therapeutic interventions, and it should be noted that data are limited with regard to gender differences in any potential class effects. Although most agents in a single therapeutic class share similar efficacy in reducing CVD risk, the safety profiles and costs may vary significantly among agents; healthcare providers should take these factors into consideration as they prescribe pharmacotherapy to prevent CVD.

The panel also emphasizes that the effectiveness of therapies prescribed in the actual office or hospital setting may vary substantially from the efficacy and safety profiles observed in clinical trials because of wide variations in patient characteristics and adherence to therapy as prescribed. Guideline development has limitations related to the generalizability of results from one population to another. The net clinical impact of an intervention may not be reflected in the scope of CVD outcomes evaluated in these guidelines. Moreover, many studies used to formulate recommendations did not include older women, especially those >80 years of age, in whom CVD and comorbidities are common. Healthcare providers should use clinical judgment about the aggressiveness of preventive interventions in all women, especially older women.

Guideline Implementation

A suggested algorithm for the prevention of CVD in women that incorporates the updated guidelines is presented in the Figure. Although a comprehensive plan to maximize implementation of the guidelines in various practice settings is beyond the scope of this document, barriers to CVD prevention should be discussed with women. A previous study by the AHA has documented numerous barriers to heart health in women; chief among them was confusion by mixed messages from the media (21). Other barriers that healthcare providers can address were as follows: 36% of women did not perceive themselves to be at risk, 25% said their healthcare provider did not say heart health was important, and 1 in 5 said healthcare providers did not clearly explain how they could change their risk status (21). Physicians have cited lack of insurance coverage as a barrier to assisting their patients with lifestyle changes (3).

Widespread documentation of lack of adherence to CVD prevention guidelines is available, even among women at high risk of CVD in managed-care settings in the United States in which access and medication coverage are available (22). Policy makers, healthcare providers, and patients all have roles to play in maximizing adherence to preventive interventions and reducing the burden of CVD. It is also important to recognize that although the causes of CVD are common to all parts of the world, the approaches to its prevention at the societal or individual level will differ among countries for cultural, social, medical, and economic reasons (23).

Research Needs and Future Directions

The expert panel suggested several gaps in knowledge related to the prevention of CVD that must be addressed to optimize the cardiovascular health of women. More rigorous testing of the impact of guidelines themselves on prevention of risk factors, slowing the progression of risk factors, and reducing the burden of CVD is needed. The development and testing of effective methods to implement guidelines in various healthcare settings, at work sites, and in communities are also research priorities. The role of communication of risk and barriers to CVD prevention should be studied and incorporated into creative methods to disseminate and implement guidelines among diverse populations of women.

The role of genetics in risk stratification and in the responsiveness to preventive interventions is an active and important area of research. Likewise, the role of gender and sex hormones requires further study to understand how they affect outcomes after interventions and how female sex may modify the prognostic value of new biomarkers and measures of subclinical CVD.

Population-wide strategies are necessary to combat the pandemic of CVD in women, because individually tailored interventions alone are likely insufficient to maximally prevent and control CVD. Public policy as an intervention to reduce gender-based disparities in CVD preventive care and improve cardiovascular outcomes among women must become an integral strategy to reduce the global burden of CVD.

TABLE 4. Guidelines for Prevention of CVD in Women: Clinical Recommendations

Lifestyle interventions

Cigarette smoking

Women should not smoke and should avoid environmental tobacco smoke. Provide counseling, nicotine replacement, and other pharmacotherapy as indicated in conjunction with a behavioral program or formal smoking cessation program *(Class I, Level B)*.

Physical activity

Women should accumulate a minimum of 30 minutes of moderate-intensity physical activity (eg, brisk walking) on most, and preferably all, days of the week *(Class I, Level B)*.

Women who need to lose weight or sustain weight loss should accumulate a minimum of 60 to 90 minutes of moderate-intensity physical activity (eg, brisk walking) on most, and preferably all, days of the week *(Class I, Level C)*.

Rehabilitation

A comprehensive risk-reduction regimen, such as cardiovascular or stroke rehabilitation or a physician-guided home- or community-based exercise training program, should be recommended to women with a recent acute coronary syndrome or coronary intervention, new-onset or chronic angina, recent cerebrovascular event, peripheral arterial disease *(Class I, Level A)*, or current/prior symptoms of heart failure and an LVEF $<40\%$ *(Class I, Level B)*.

Dietary intake

Women should consume a diet rich in fruits and vegetables; choose whole-grain, high-fiber foods; consume fish, especially oily fish,* at least twice a week; limit intake of saturated fat to $<10\%$ of energy, and if possible to $<7\%$, cholesterol to <300 mg/d, alcohol intake to no more than 1 drink per day,† and sodium intake to <2.3 g/d (approximately 1 tsp salt). Consumption of *trans*-fatty acids should be as low as possible (eg, $<1\%$ of energy) *(Class I, Level B)*.

Weight maintenance/reduction

Women should maintain or lose weight through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m^2 and a waist circumference ≤ 35 in *(Class I, Level B)*.

Omega-3 fatty acids

As an adjunct to diet, omega-3 fatty acids in capsule form (approximately 850 to 1000 mg of EPA and DHA) may be considered in women with CHD, and higher doses (2 to 4 g) may be used for treatment of women with high triglyceride levels *(Class IIb, Level B)*.

Depression

Consider screening women with CHD for depression and refer/treat when indicated *(Class IIa, Level B)*.

Major risk factor interventions

Blood pressure—optimal level and lifestyle

Encourage an optimal blood pressure of $<120/80$ mm Hg through lifestyle approaches such as weight control, increased physical activity, alcohol moderation, sodium restriction, and increased consumption of fresh fruits, vegetables, and low-fat dairy products *(Class I, Level B)*.

Blood pressure—pharmacotherapy

Pharmacotherapy is indicated when blood pressure is $\geq 140/90$ mm Hg or at an even lower blood pressure in the setting of chronic kidney disease or diabetes ($\geq 130/80$ mm Hg). Thiazide diuretics should be part of the drug regimen for most patients unless contraindicated or if there are compelling indications for other agents in specific vascular diseases. Initial treatment of high-risk women‡ should be with β-blockers and/or ACE inhibitors/ARBs, with addition of other drugs such as thiazides as needed to achieve goal blood pressure *(Class I, Level A)*.

Lipid and lipoprotein levels—optimal levels and lifestyle

The following levels of lipids and lipoproteins in women should be encouraged through lifestyle approaches: LDL-C <100 mg/dL, HDL-C >50 mg/dL, triglycerides <150 mg/dL, and non–HDL-C (total cholesterol minus HDL cholesterol) <130 mg/dL *(Class I, Level B)*. If a woman is at high risk‡ or has hypercholesterolemia, intake of saturated fat should be $<7\%$ and cholesterol intake <200 mg/d) *(Class I, Level B)*.

Lipids—pharmacotherapy for LDL lowering, high-risk women

Utilize LDL-C–lowering drug therapy simultaneously with lifestyle therapy in women with CHD to achieve an LDL-C <100 mg/dL *(Class I, Level A)* and similarly in women with other atherosclerotic CVD or diabetes mellitus or 10-year absolute risk $>20\%$ *(Class I, Level B)*.

A reduction to <70 mg/dL is reasonable in very-high-risk women§ with CHD and may require an LDL-lowering drug combination *(Class IIa, Level B)*.

Lipids—pharmacotherapy for LDL lowering, other at-risk women

Utilize LDL-C–lowering therapy if LDL-C level is ≥ 130 mg/dL with lifestyle therapy and there are multiple risk factors and 10-year absolute risk 10% to 20% *(Class I, Level B)*.

Utilize LDL-C–lowering therapy if LDL-C level is ≥ 160 mg/dL with lifestyle therapy and multiple risk factors even if 10-year absolute risk is $<10\%$ *(Class I, Level B)*.

Utilize LDL-C–lowering therapy if LDL ≥ 190 mg/dL regardless of the presence or absence of other risk factors or CVD on lifestyle therapy *(Class I, Level B)*.

Lipids—pharmacotherapy for low HDL or elevated non–HDL, high-risk women

Utilize niacin‖ or fibrate therapy when HDL-C is low or non–HDL-C is elevated in high-risk women‖ after LDL-C goal is reached *(Class IIa, Level B)*.

Lipids—pharmacotherapy for low HDL or elevated non-HDL, other at-risk women

Consider niacin‖ or fibrate therapy when HDL-C is low or non–HDL-C is elevated after LDL-C goal is reached in women with multiple risk factors and a 10-year absolute risk 10% to 20% *(Class IIb, Level B)*.

Diabetes mellitus

Lifestyle and pharmacotherapy should be used as indicated in women with diabetes *(Class I, Level B)* to achieve an HbA_{1C} $<7\%$ if this can be accomplished without significant hypoglycemia *(Class I, Level C)*.

TABLE 4. Continued

Preventive drug interventions
Aspirin, high risk
Aspirin therapy (75 to 325 mg/d)¶ should be used in high-risk‡ women unless contraindicated *(Class I, Level A)*.
If a high-risk‡ woman is intolerant of aspirin therapy, clopidogrel should be substituted *(Class I, Level B)*.
Aspirin—other at-risk or healthy women
In women ≥65 years of age, consider aspirin therapy (81 mg daily or 100 mg every other day) if blood pressure is controlled and benefit for ischemic stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke *(Class IIa, Level B)* and in women <65 years of age when benefit for ischemic stroke prevention is likely to outweigh adverse effects of therapy *(Class IIb, Level B)*.
β-Blockers
β-Blockers should be used indefinitely in all women after MI, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated *(Class I, Level A)*.
ACE inhibitors/ARBs
ACE inhibitors should be used (unless contraindicated) in women after MI and in those with clinical evidence of heart failure or an LVEF ≤40% or with diabetes mellitus *(Class I, Level A)*. In women after MI and in those with clinical evidence of heart failure or an LVEF ≤40% or with diabetes mellitus who are intolerant of ACE inhibitors, ARBs should be used instead *(Class I, Level B)*.
Aldosterone blockade
Use aldosterone blockade after MI in women who do not have significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and β-blocker, and have LVEF ≤40% with symptomatic heart failure *(Class I, Level B)*.

LVEF indicates left ventricular ejection fraction; BMI, body mass index; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CHD, coronary heart disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CVD, cardiovascular disease; and MI, myocardial infarction.

*Pregnant and lactating women should avoid eating fish potentially high in methylmercury (eg, shark, swordfish, king mackerel, or tile fish) and should eat up to 12 oz/wk of a variety of fish and shellfish low in mercury and check the Environmental Protection Agency and the US Food and Drug Administration's Web sites for updates and local advisories about safety of local catch.

†A drink equivalent is equal to a 12-oz bottle of beer, a 5-oz glass of wine, or a 1.5-oz shot of 80-proof spirit.

‡Criteria for high risk include established CHD, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, end-stage or chronic renal disease, diabetes mellitus, and 10-year Framingham risk >20%.

§Criteria for very high risk include established CVD plus any of the following: multiple major risk factors, severe and poorly controlled risk factors, diabetes mellitus (19).

‖Dietary supplement niacin should not be used as a substitute for prescription niacin.

¶After percutaneous intervention with stent placement or coronary artery bypass grafting within previous year and in women with noncoronary forms of CVD, use current guidelines for aspirin and clopidogrel (20).

TABLE 5. Class III Interventions (Not Useful/Effective and May Be Harmful) for CVD or MI Prevention in Women

Menopausal therapy
Hormone therapy and selective estrogen-receptor modulators (SERMs) should not be used for the primary or secondary prevention of CVD *(Class III, Level A)*.
Antioxidant supplements
Antioxidant vitamin supplements (eg, vitamin E, C, and beta carotene) should not be used for the primary or secondary prevention of CVD *(Class III, Level A)*.
Folic acid*
Folic acid, with or without B6 and B12 supplementation, should not be used for the primary or secondary prevention of CVD *(Class III, Level A)*.
Aspirin for MI in women <65 years of age†
Routine use of aspirin in healthy women <65 years of age is not recommended to prevent MI *(Class III, Level B)*.

CVD indicates cardiovascular disease; MI, myocardial infarction.

*Folic acid supplementation should be used in the childbearing years to prevent neural tube defects.

†For recommendation for aspirin to prevent CVD in women ≥65 years of age or stroke in women <65 years of age, please see Table 4.

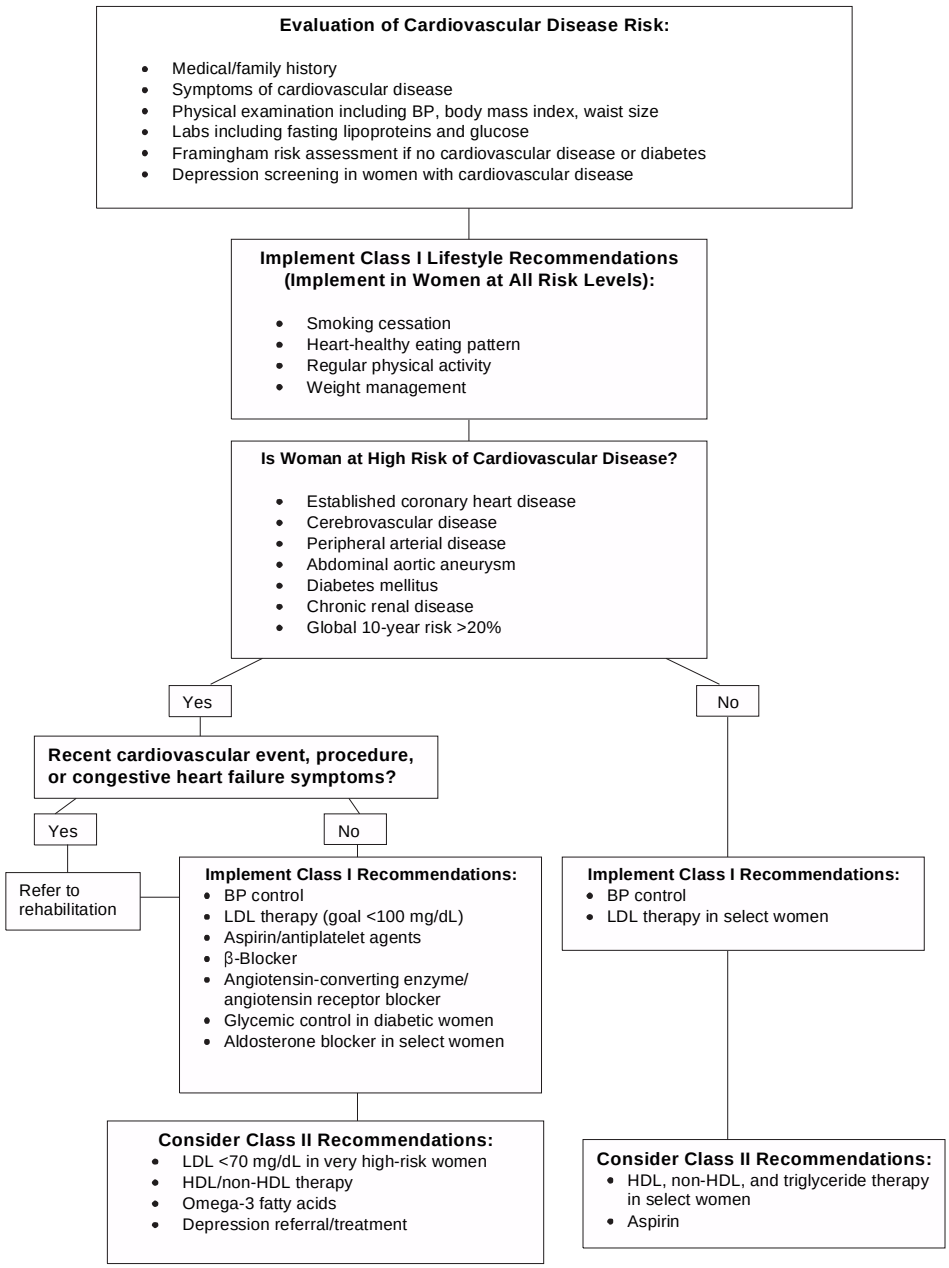

Figure. Algorithm for CVD preventive care in women. Labs indicates laboratory tests; BP, blood pressure; LDL, low-density lipoprotein cholesterol; and HDL, high-density lipoprotein cholesterol.

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Hyperlipidemia

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None reported.

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*Modest.

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Stroke Rehabilitation

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Appendix 7

A New Perspective on Nonprescription Statins: An Opportunity for Patient Education and Involvement

Valentin Fuster, MD, PhD*

Education of the public and encouragement of patients' involvement in their own health care have been repeatedly proved effective means of increasing health awareness, promoting lifestyle modifications, and improving early disease detection in a variety of clinical scenarios. Despite substantial efforts from different public and private organizations to educate the population on cardiovascular risk, coronary heart disease remains the leading cause of death in the United States, and its prevalence continues to grow. Therefore, alternative approaches with the potential to elicit a meaningful impact in the community deserve consideration. A nonprescription statin program could provide consumers with a tool of proved benefit in cardiovascular risk prevention. The magnitude of the target population (millions of subjects with intermediate to high risk), as well as the safety and efficacy profile of lovastatin 20 mg, support the consideration of this drug for "over-the-counter" availability. Moreover, a nonprescription statin program could represent a unique opportunity not only to enhance patients' involvement in primary prevention but also to reinforce the education of the public and to encourage interaction with health care providers. The success of such a program will undoubtedly require precise labeling of the risks and benefits of the therapy, as well as active support and participation from major medical organizations. In conclusion, nonprescription statin availability, through enhanced unique patients' involvement, offers the potential for enormous public health benefit. **(Am J Cardiol 2007;100:907–910)**

Despite advances in the treatment of coronary heart disease (CHD) that have reduced the mortality rate, CHD remains a major cause of mortality and disability in the United States. It is estimated that the number of Americans with CHD will more than double (to 30 million) by 2050.[1] In response, the National Heart, Lung, and Blood Institute issued updated guidelines in 2001 (amended for higher risk patients in 2004) for the detection, evaluation, and treatment of high blood cholesterol (known as the Adult Treatment Panel III guidelines), including those at moderate risk without CHD.[2,3] The U.S. population in 2000 (aged 20 to 79 years) was estimated to include 23 million subjects without CHD (or CHD equivalents) but with a 10% to 20% risk for developing CHD within 10 years.[4] Although not all, a large proportion of them are candidates for lipid-lowering therapy according to the Adult Treatment Panel III guidelines.[3] Despite the endorsement of these guidelines by all major medical organizations, many of these eligible subjects are not being treated, and approaches to close this treatment gap have had limited success.[5] In 2001, the National Academy of Science's Institute of Medicine concluded that dramatic and innovative changes in the U.S. health care system are necessary to combat this and other treatment gaps. One of the themes for change recommended by the Institute of Medicine is the need for increased consumer participation in their own health care.[6]

Patient Education Enhances Participation in Primary Prevention

Patient education and participation strategies have demonstrated success in other therapeutic areas, in which significant narrowing of treatment gaps occurred once patients were equipped with increased awareness, education, and tools to assist in diagnosis and treatment. Campaigns in the 1970s and 1980s warning of the dangers of hypertension, coupled with widespread access to blood pressure monitoring devices, changed not only the awareness but also the treatment of this "silent killer."[7] In the 1990s, smoking cessation attempts greatly increased as a result of educational campaigns, the adoption of nonsmoking policies, and easy access to nonprescription nicotine replacement therapies.[8] Similarly, the early detection of cancer, especially breast cancer, has greatly benefited from education initiatives and patient self-assessment tools.[9]

As past president of the World Heart Federation, I have observed in developing countries the public health benefits of educating individuals on health matters rather than relying solely on the implementation of physician guidelines. Currently, the World Heart Federation is working with the Ministry of Health for Grenada to develop community participatory and patient self-management programs that assist local health care providers in risk factor detection, treatment, and control. Given that nation's limited health care resources, the prevention of a CHD epidemic in Grenada will require such patient-provider partnerships.

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This approach could have similar results with CHD prevention efforts in the United States. The Adult Treatment Panel III guidelines are written for physicians, but we also need a corresponding effort directed at educating consumers. Public awareness and education efforts of the American Heart Association, the National Institutes of Health, and others are laudable. They have helped foster significant public interest in maintaining or improving cardiovascular health, provided the public with information to better understand cardiovascular risk, and encouraged discussion about CHD risk reduction with health care providers. Despite these efforts, a substantial proportion of subjects with treatable cardiovascular risk factors remain either unaware of their conditions, untreated, or inadequately controlled.[5] Thus, to achieve meaningful reductions in CHD mortality and morbidity, new approaches deserve consideration. A nonprescription statin program could augment existing efforts by enhancing personal involvement in CHD risk reduction, additionally providing subjects with further guidance about the management of their cardiovascular health, and enhancing access to testing and treatment. Thus, although it is clear that awareness and education are critical components of any CHD prevention program, providing consumers with a tool with proved benefit, namely a statin drug, can substantially improve the opportunity to achieve a successful outcome of CHD risk reduction at the individual and population levels.

The Proposal for Nonprescription Statins

Although there is general agreement regarding the need for increased treatment in many subjects with 10% to 20% CHD risk,[10] there is no consensus regarding the best approach. A recent debate centered on a proposal for the nonprescription availability of low-dose statins for reducing CHD risk. The issues were discussed at a joint meeting of the U.S. Food and Drug Administration's Endocrinologic and Metabolic Drugs Advisory Committee and Nonprescription Drugs Advisory Committee in January 2005 regarding an application for nonprescription lovastatin 20 mg.[11] The committees unanimously agreed that the target population, efficacy, and safety profile of lovastatin 20 mg (including the potential for muscle toxicity, drug interactions, and the lack of a liver function testing requirement) were acceptable for nonprescription use. The advisory committees also concluded that pregnancy risks in a nonprescription setting could be adequately addressed through more effective label warnings and recommended that the drug's use be restricted to women aged $\geq$54 years.

Further evidence supporting the use of low-dose statins was presented to the committees suggesting that the benefit-to-risk relation is as good as that for nonprescription low-dose aspirin. Over 5 years of treatment, CHD risk reduction is similar, while the potential for a serious adverse event with lovastatin is less than that with aspirin.[12] Much of the supporting safety data presented to the committees were derived from the extensive postmarketing experience accumulated since lovastatin was introduced in the mid-1980s. The rationale for benefit of the 20-mg dose in the targeted moderate-risk population was established by the landmark Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), which demonstrated significant CHD risk reduction over a 5.2-year treatment period.[13,14] Given these areas of consensus, the 2005 advisory committee debate ultimately centered on appropriate consumer self-identification and whether nonprescription statin programs could facilitate consumer education and participation in preventing CHD. Committee members lauded the effort and progress made regarding consumer behavior with nonprescription lovastatin. However, they voted that consumer self-diagnosis and self-selection needed further evaluation, with revised labeling that better communicates benefit and risk.[11]

Numerous viewpoints and discussions have appeared since the joint advisory committee meeting concerning nonprescription lovastatin.[15–20] These reports have examined statins in the context of the current nonprescription model in the United States and suggested numerous challenges. Unfortunately, on the benefit side of the equation, the authors of these reports disregarded the potential for broader patient education and participation. In addition to the opportunity to enhance patients' involvement in primary prevention through increased access to effective tools for the diagnosis and treatment of high cholesterol, another real value of the nonprescription statin proposal lies in the potential to offer a new approach to educating individuals.

The Educational Opportunity

Although the 2005 advisory committee vote on overall approval of nonprescription lovastatin was negative, the committee members agreed on the importance of effective consumer education for a nonprescription statin to have a positive impact on CHD prevention. The lovastatin nonprescription program presented at the advisory committee meeting was intended to drive appropriate consumer action through increased awareness, understanding, access to assessment and behavior modification tools, and health care professional interaction. The program included components aimed at (1) educating users before purchase to increase heart health awareness, assisting consumers with initial cardiovascular treatment assessment, and encouraging consumers to act; (2) emphasizing the importance of diet, exercise, and other lifestyle changes, obtaining follow-up cholesterol tests, and reaching the appropriate cholesterol goal; and (3) encouraging continued interaction with pharmacists and physicians regarding the appropriate use of nonprescription and prescription statins.

Key elements of the program include education-oriented mass media advertising, informational and self-assessment materials, toll-free services, Web sites, newsletters, and e-mails designed to encourage and facilitate appropriate self-management and interaction with health care professionals.

This approach represents a significant advance beyond currently marketed nonprescription products and was fully tested in an actual-use study, the Consumer Use Study of OTC Mevacor (CUSTOM).[21] In this study, $>$1,000 consumers purchased lovastatin 20 mg in a simulated retail setting and were followed for up to 6 months. There were no significant safety concerns, most participants got cholesterol tests and reached their treatment goals, and the overall 21%

to 24% reduction in low-density lipoprotein cholesterol was comparable with results obtained in controlled trials. The results further suggested that the educational materials increased awareness regarding cardiovascular health and effectively helped subjects recognize when they were ineligible for nonprescription statin therapy. More than 90% of participants maintained or improved their dietary and exercise habits, and >60% of participants persisted with therapy for the entire study, which compares favorably with prescription use data.[22] Importantly, most patients in CUSTOM reported that health care professional interactions were maintained or improved during the study.[23]

CUSTOM demonstrated how nonprescription statins could augment current CHD prevention efforts by educating and involving consumers. However, the Food and Drug Administration and the advisory committees expressed concern that a substantial proportion of the CUSTOM participants who purchased and used the product were ineligible according to the label, particularly those at lower CHD risk. This potential could be minimized through the development of more emphatic labeling language and by providing users with a better understanding of the factors contributing to CHD risk and the appropriateness of self-treatment.[11] Therefore, it is incumbent on pharmaceutical industry sponsors to accept and address the challenge to revise and test improved labeling.

Developments

Since the January 2005 advisory committee meeting, new findings have been published regarding the potential public health benefit of nonprescription statins. A recent analysis looked at CUSTOM study participants' CHD risk factors and the relative risk reduction expected from the use of lovastatin 20 mg. The findings were extrapolated to determine the predicted public health benefit of nonprescription statin availability on CHD morbidity and mortality. This analysis concluded that there is likely to be a strong population benefit of nonprescription therapy, even if a modest level of diversion from optimal prescription care is assumed.[23] More recently, a comprehensive review of statin safety[24] concluded that statins are remarkably safe, especially at the lower end of the dose range. The results of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study[25] in Japan corroborate the AFCAPS/TexCAPS findings by also demonstrating significant CHD risk reduction associated with a low-dose statin (pravastatin 10 to 20 mg) in a primary prevention population.

In January 2006, the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee met again on another product proposed for nonprescription status: orlistat 60 mg to promote weight loss in overweight adults. Unlike the vote on nonprescription statins, committee members voted favorably for nonprescription status for orlistat. Acknowledging the obvious differences in the conditions, the drug characteristics, and the duration of therapy, it remains interesting to compare similarities between the nonprescription orlistat and lovastatin proposals to gain some understanding of the different advisory committee outcomes.

Obesity and hyperlipidemia represent serious public health issues for which current approaches have been inadequate. Also, despite intense consumer interest in the self-management of obesity and hyperlipidemia, there are no safe, effective, Food and Drug Administration–approved, nonprescription alternatives to widely used, but unproved, dietary supplements. Finally, the proposed nonprescription programs for orlistat and lovastatin rely on comprehensive education and support rarely seen with nonprescription products. These programs can provide additional public health value by educating consumers not only on drug therapy but also on the conditions being treated, the overall risk/benefit ratio, and complementary diet and exercise regimens.

An important difference between the lovastatin and orlistat proposals affecting the advisory committee deliberations was the public forum. Major medical and public health groups provided strong support and testimony for nonprescription orlistat and its educational approach to weight loss. At the lovastatin meeting, several advocates endorsed the concept, but a similar show of support was notably missing from key organizations with major stakes in the primary prevention of cardiovascular disease.

A Call to Action

Examples from the nonprescription lovastatin program studied in CUSTOM provide glimpses of the potential positive impact that nonprescription statins could have on the education and involvement of at-risk subjects in the prevention of CHD. Most of the January 2005 advisory committee members commended the effort and encouraged further research while voting against approval of the nonprescription program as presented. The joint committee chair, Alistair Wood, formerly an associate dean at Vanderbilt University, in his dissent from the majority opinion stated that "lowering the populations' cholesterol by just a little bit produces a huge public health advantage."[11]

Without increased patient education and access to diagnostic and treatment tools, progress on the CHD epidemic will remain stalled. Clear advantages to increased patient participation, education, and responsibility for major public health issues have been proved repeatedly. Nonprescription statins could positively affect efforts toward increased patient education and participation regarding the primary prevention of CHD. Consumer-friendly diagnostic and treatment tools regarding lipid management and CHD risk reduction that would doubtless accompany nonprescription statins could motivate millions to take actions such as getting cholesterol tests, adopting healthier lifestyles, and discussing cholesterol management with health care professional. To realize this potential, sponsors of nonprescription statin proposals must continue the development of improved product labeling and educational messages and to demonstrate their effectiveness in driving appropriate consumer behavior.

Despite much agreement in the 2005 advisory committee meeting and the addressing of most concerns by data from consumer and clinical research, the input of major medical and public health groups has been sparse and noncommittal during this critical debate. How do we, as leaders in the

primary prevention effort, help support and shape the discussion around this potentially valuable proposal as part of a broader primary prevention patient education and participation initiative? The value of support from major medical groups was apparent from the orlistat deliberations and helped create a positive environment for discussion and eventual endorsement. Without similarly strong support from the medical community, it is unclear if the nonprescription statin initiative will continue to be evaluated.

There will always be skepticism and hesitancy when examining new approaches, but the public health challenge demands breaking down these initial barriers to explore novel opportunities. The cardiology community should lead a more public discussion of how nonprescription statins could become a component of a primary prevention patient education and participation strategy and, in so doing, take much needed action toward alleviating the CHD epidemic.

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Appendix 8

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.**

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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 $\geq$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 $\geq$80% for self-selection and $\geq$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 $\geq$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.

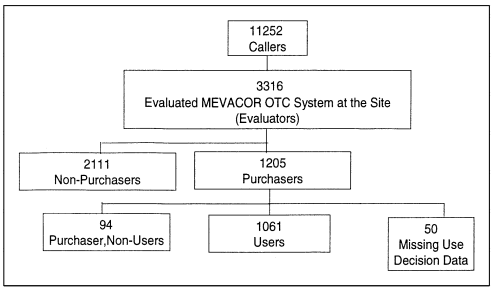

FIGURE 1. Participant flow through the study.

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.

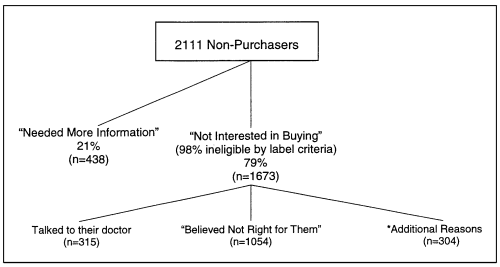

FIGURE 2. Nonpurchaser behavior. *Includes remaining participants who provided (n = 283) or did not provide (n = 21) a reason for deciding not to purchase.

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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Appendix 9

Potential Impact on Cardiovascular Public Health of Over-the-Counter Statin Availability

Eric P. Brass, MD, PhD[a,*], Shannon E. Allen, PhD[b], and Jeffrey M. Melin, MD[b]

Over-the-counter (OTC) statin availability has been hypothesized to represent a strategy for treating consumers at moderate risk of coronary heart disease (CHD) who are currently not receiving drug therapy. The viability of this strategy has been questioned, particularly with respect to the public health benefit that can be obtained in an unsupervised treatment environment. The previously reported Consumer Use Study of Over-the-Counter Lovastatin (CUSTOM) examined consumer behavior in a simulated OTC setting in which 20 mg lovastatin could be purchased. Framingham CHD risk scores were calculated for 981 self-selected consumers who used OTC lovastatin in CUSTOM. Overall, this group had a median 10-year CHD risk of 10%, but with significant numbers of consumers with estimated risks of < 5% and > 20%. According to the risk profile of CUSTOM consumers, the use of 20 mg lovastatin for 10 years would be expected to prevent approximately 33,100 CHD events per 1 million users. This represents a 10-year number needed to treat of 30 consumers. This optimal benefit may be reduced because some higher risk consumers in CUSTOM used lovastatin rather than appropriate, more aggressive supervised care. On the basis of the frequencies of diversion from optimal care observed in CUSTOM, the number of events prevented might be reduced to 23,000 (number needed to treat 43 consumers). Sensitivity analyses have demonstrated that these estimates are robust and that the predicted public health benefit likely falls in the range of 23,000 to 33,000 CHD events prevented per 1 million treated for 10 years. In conclusion, on a population basis, OTC statin availability is likely to result in clinically meaningful reductions in CHD morbidity and mortality. The analyses also identified opportunities for optimizing the use of OTC statins in the marketplace. **(Am J Cardiol 2006;97:851–856)**

Making 3-hydroxy-3-methylglutaryl-co-enzyme A reductase inhibitors (statins) available through over-the-counter (OTC) sales has been suggested as an effective strategy to help address the public health problem of coronary heart disease (CHD).[1] This strategy is based on the proven ability of statins to prevent CHD events (myocardial infarction and coronary deaths)[2,3] and the inability of the healthcare system to facilitate access to statins for all those who might benefit from treatment.[1,4–6] OTC statin availability might remove some of the barriers to statin therapy. On the basis of this reasoning, simvastatin (10 mg) has been available without a prescription in the United Kingdom since 2004.[7]

This theoretical public health benefit from OTC availability might not be realized because of the inability of consumers to self-manage their cholesterol or could be offset through the use of OTC statins by patients for whom such therapy would be inappropriate. The Consumer Use Study of Over-the-Counter Lovastatin (CUSTOM)[8] was conducted under conditions simulating the OTC marketplace, and thus allowed the profile of consumers likely to use statins in an uncontrolled OTC setting and their behaviors with respect to lipid management to be approximated.

Methods

Design of CUSTOM: The details of the CUSTOM have been previously reported.[8] This study was designed to quantify consumer behaviors in a simulated OTC environment in which lovastatin (20 mg) was available for purchase. Patients were recruited through media advertising and could visit a study site simulating a pharmacy setting. Participants could elect to purchase the OTC lovastatin (Mevacor OTC) or leave without purchasing. Of 3,316 consumers who visited the study sites, 1,061 bought and used OTC lovastatin. Core demographic information and a baseline lipid profile were obtained for each purchaser. The study sites remained open for consumers to purchase additional drug supplies during the course of the study.

Estimation of CHD risk: Participants' 10-year CHD risk (myocardial infarction or coronary death) was esti-

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Table 1
Estimated coronary heart disease (CHD) events prevented in CUSTOM population during 10 years of treatment

Risk Strata	Fraction of CUSTOM Users in Stratum	Predicted Events in Untreated CUSTOM Users	Events Prevented With OTC Lovastatin
0–5% (2.5%)	0.29	7,250	1,812
5–10% (7.5%)	0.19	14,250	3,562
10–20% (15%)	0.28	42,000	10,500
20–25% (22.5%)	0.04	9,000	2,250
>25% (30%)	0.03	9,000	2,250
Pre-existing condition* (30%)	0.17	51,000	12,750
Total	1.00	132,000	33,124

Framingham CHD risks were calculated for 981 CUSTOM participants who used OTC lovastatin. Cohorts were formed based on risk strata, and events prevented calculated based on 25% relative risk reduction. Numbers are normalized to a population of 1 million. Data in parentheses are 10-year risks used for calculation purposes in each stratum.

* Established CHD, stroke, or diabetes.

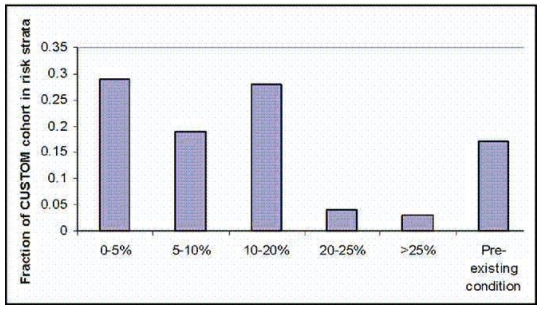

Figure 1. Framingham 10-year CHD risk estimates for CUSTOM cohort. Framingham risk scores were calculated for 981 evaluable CUSTOM participants (see text for details). Fraction of total number of patients in each risk stratum shown.

mated using the Framingham Point Scoring System.[9] Age, gender, and smoking status were self-reported. Total cholesterol and high-density lipoprotein (HDL) cholesterol were measured at the OTC purchase. The measured lipid concentrations were not made available to the study participants, in keeping with the simulated OTC setting. Blood pressure was measured at the study site. For the 1,061 OTC lovastatin users, 981 subjects had all data elements required to calculate the risk profiles (69 had missing data precluding calculation of risk, 9 were >79 years and thus could not be assessed using the Framingham model, and 2 were protocol violators). Those users with a Framingham risk of >20% or a preexisting condition (diabetes mellitus or established cardiovascular disease) were characterized as the higher risk subgroup.

Estimation of treatment efficacy: Lovastatin 20 mg has been extensively studied in clinical trials and has consistently been associated with approximately a 25% reduction in low-density lipoprotein (LDL) cholesterol concentrations.[10,11] A similar reduction was observed in CUSTOM.[8] Lovastatin has been shown to decrease CHD events by 30% to 40% (depending on end point definition) when used for primary prevention in patients at moderate risk of coronary disease[11,12] and in a study subset approximating an OTC target population.[12] The results with lovastatin in primary prevention have also been consistent with the general finding across all cholesterol-lowering trials that each 1% reduction in LDL cholesterol is associated with an approximately 1% relative risk reduction for CHD events.[3] Thus, for modeling purposes in the present analyses, it was conservatively estimated that use of 20 mg lovastatin OTC would be associated with a 25% relative risk reduction for CHD events.

Increased LDL cholesterol lowering can be achieved with higher statin doses, and such therapy would be appropriate for higher risk patients. According to the results of available clinical trials and the LDL–CHD risk reduction relation previously mentioned, a 50% relative risk reduction was used to model the efficacy of optimal, supervised hypercholesterolemia management. This estimate for risk reduction is at least as large as that observed in a range of clinical trials[13–15] and allows for the larger reduction that might be anticipated with more aggressive LDL targets.[16]

Estimation of net CHD event reduction: For the present analyses, the CUSTOM cohort with defined CHD risk estimates was used to estimate the profile of an OTC statin user population, normalized for convenience to a total population of 1 million OTC users. The group was divided into risk strata (Table 1) for ease of presentation and clarity, and each stratum was assigned a specific absolute CHD risk (estimated as the midpoint of the range or 30% for the highest risk cohorts). The number of CHD events prevented by OTC statin treatment was calculated on the basis of the risk determined from the Framingham risk score and the relative risk reductions presented previously. The number needed to treat was calculated as the reciprocal of the absolute risk reduction.

OTC statin use could theoretically be associated with a net increase in CHD events if the comparator group included patients receiving optimal, aggressive statin therapy, rather than simply being untreated. Any cohort of OTC users would include patients who used an OTC statin rather than no therapy, and others for whom the OTC statin was a diversion from supervised prescription therapy. Therefore, the number of potential excess events for these diverted patients was calculated as the difference between the estimated events prevented with optimal therapy (if used) minus the number prevented with OTC treatment. The net CHD events prevented with OTC availability was then calculated as the number of events prevented in the subset of the total user population for whom OTC statin use replaced no therapy minus the excess events in the

subgroup using OTC therapy in place of optimal, supervised therapy.

Results

Risk and projected cardiovascular events in CUSTOM cohort: The OTC label used in CUSTOM was designed to allow consumers with indications for statin treatment and a LDL cholesterol goal of <130 mg/dl, as defined by the National Cholesterol Education Program Adult Treatment Panel III report,[9] to self-select OTC lovastatin and manage their hypercholesterolemia. Framingham 10-year risk scores[9] were calculated for 981 CUSTOM participants, and the participants were grouped by risk strata (Figure 1). Approximately 50% of the participants had a 10-year risk of 5% to 25%. Twenty percent of the participants had 10-year risks >25%, mostly associated with preexisting conditions (i.e., established coronary heart disease, stroke, or diabetes). A large number of participants had a 10-year risk of <5%, primarily resulting from consumers younger than the label age cutoff electing to use OTC lovastatin. Overall, the CUSTOM users had a median 10-year estimated CHD event rate of 10%.

The risk stratification observed in the CUSTOM user cohort can be used to estimate the public health effect of OTC lovastatin availability in the general marketplace. The magnitude of LDL cholesterol lowering observed in CUSTOM would be predicted to result in a 25% relative risk reduction in CHD events.[3] On the basis of the 10-year Framingham risks calculated, the use of OTC lovastatin would result in the prevention of 33,124 CHD events per 1 million users within 10 years (Table 1). For the total cohort, this represented a number needed to treat of 30 consumers. Although the relative risk reduction was constant across the risk strata, the absolute risk reduction varied enormously. Thus, in the cohort with preexisting conditions, the number needed to treat to prevent a CHD event was only 13 consumers, and in the lowest risk group (0% to 5%), the corresponding number was 160.

Factors potentially offsetting public health benefit of OTC lovastatin: The previously mentioned analysis was based on a comparison of OTC lovastatin versus no lipid-lowering drug therapy. However, this might not be the case in an unsupervised setting. The National Cholesterol Education Program Adult Treatment Panel III report has recommended that patients with a 10-year Framingham risk of >20% or preexisting conditions (i.e., stroke, established coronary heart disease, or diabetes) be treated to a LDL cholesterol of ≤100 mg/dl.[3,9] Such a target would be unlikely to be met with 20 mg lovastatin for the higher risk cohort in CUSTOM (in contrast to the lower risk groups with a target of 130 mg/dl who would be likely to reach that target at OTC doses). To the degree that consumers use OTC lovastatin instead of supervised, optimal statin therapy, the result would be an excess of CHD events in a public health model. This diversion from optimal therapy has been discussed as a major concern if OTC statins were to be made available.[17–19]

Table 2
CHD event prevention in the higher risk CUSTOM cohort

Scenario	Net CHD Events Prevented (10-yr treatment of 240,000 higher risk consumers)
OTC vs no therapy	17,250
Optimal therapy vs no therapy	34,500
OTC therapy with 12% diversion rate	13,110
OTC therapy with 30% diversion rate	6,900
OTC therapy plus 10% upgraded to optimal therapy vs. no therapy	18,480
OTC therapy with 12% diversion rate and 10% upgraded to optimal therapy	14,450

Twenty-four percent of the CUSTOM cohort had a 10-year event risk of >20% or had a pre-existing condition (established CHD, stroke, or diabetes) and thus would contribute 240,000 consumers to a modeled risk cohort of 1,000,000. Impact of OTC therapy (25% relative risk reduction), optimal-supervised therapy (50% relative risk reduction), diversion from optimal therapy to OTC therapy (resulting in excess events), and self-triage upgrade to optimal care based on the OTC experience (further risk reduction) are illustrated.

Data from CUSTOM allowed the effect of diversion from optimal care to be understood in the context of public health outcomes. Diversion from optimal care may result from 2 types of consumer behaviors. First, patients already on prescription, supervised, lipid-lowering therapy might discontinue this therapy and begin OTC self-management. Alternatively, a previously untreated, higher risk consumer might elect to choose an OTC option instead of seeking supervised care.

Despite label warnings, 30% of the higher risk CUSTOM cohort substituted lovastatin OTC for prescription lipid-lowering therapy. Of note, 60% of these participants on prescription therapy (or 18% of the total higher risk cohort) consulted with their physician before using OTC lovastatin, suggesting that these patients might not represent true diversions. The impact of diversion on the higher risk subgroup was analyzed with respect to the CHD outcomes (Table 2). The use of 20 mg lovastatin versus no therapy would have prevented 17,250 CHD events per 240,000 higher risk OTC users (i.e., among 24% of the modeled 1 million CUSTOM users [Table 1]). This would be in addition to the 15,874 events prevented in the lower and moderate risk CUSTOM subsets. If 100% of these 240,000 higher risk consumers received the 50% relative risk reduction projected with optimal, supervised care, 34,500 CHD events would have been prevented; thus, OTC availability could be viewed as having resulted in an excess of 17,250 CHD events. However, if the prescription-to-OTC substitution rate was 30% (the worst case scenario projected from CUSTOM), 6,900 net events would still have been prevented among the higher risk subjects after allowing for the excess events resulting from suboptimal therapy. If a

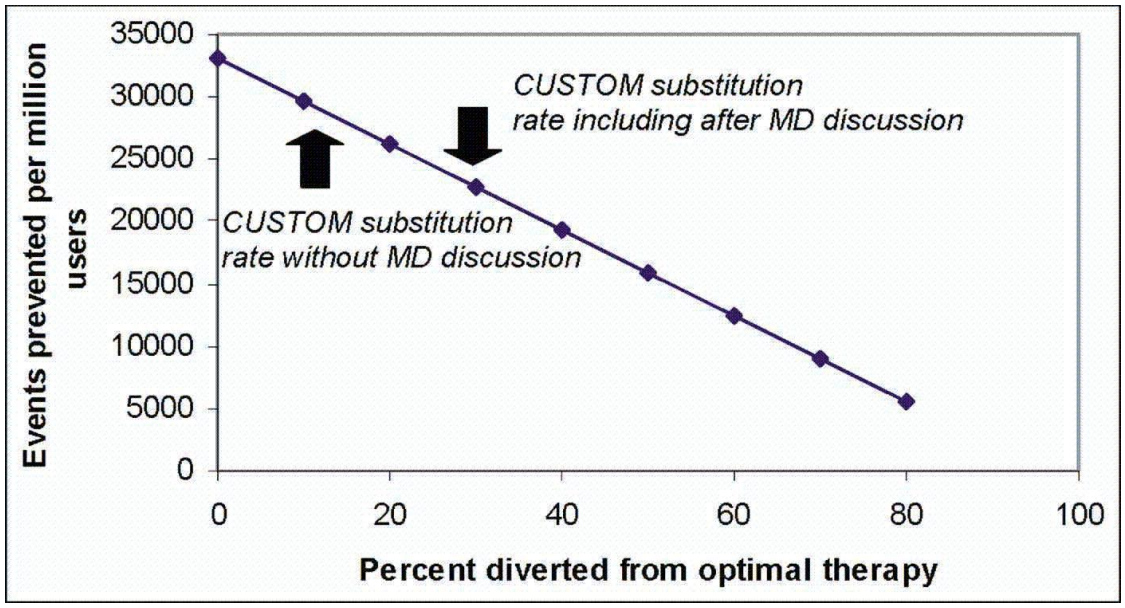

Figure 2. Impact of diversion rates from optimal care on net events prevented. CHD events prevented with OTC statin use depicted per 1 million OTC users, with CHD risk distributed as for CUSTOM participants. Net benefit reduced by diversion of higher risk consumers from optimal, supervised care resulting from availability of OTC statins. *Large arrows*, range of possible diversion rates estimated in CUSTOM.

Table 3
Sensitivity analysis of higher risk consumer contribution to treated population and rates of diversion from optimal therapy on CHD event prevention with OTC lovastatin

Percentage of Higher Risk Users Diverted	No. of Events Prevented per 1 Million Treated (percentage of total population at higher risk)		
	15%	24%	35%
0%	27,500	33,124	37,500
12%	24,980	28,984	31,620
30%	21,200	22,774	22,800
40%	19,100	19,324	17,900

OTC therapy was modeled to cause a 25% relative risk reduction, and optimal therapy, a 50% risk reduction. Predicted event rates of 8% in the non–higher-risk subset and 28% in the higher risk subset, as were observed in CUSTOM, were used. In CUSTOM, the higher risk subset was 24% of the total population, and diversion from this group was estimated at 12% if only substitution without physician contact was considered, 30% if all prescription lipid therapy was considered, and 40% if the worst case for substitution was used plus an additional 10% were considered to have started OTC treatment rather than seeking supervised care.

12% substitution rate was used (the conservative rate according to the CUSTOM results), the net events prevented would be 13,110. In these 2 cases, this net benefit would be in addition to the 15,874 events prevented in the lower risk cohorts.

The rate of diversion from optimal care resulting from untreated higher risk patients selecting an OTC option because it is available, rather than seeking optimal supervised care, could not be accurately estimated from CUSTOM. However, the high degree of participant–physician interaction in CUSTOM[8,20] suggested that this type of diversion was not common. Using the population risk distribution from CUSTOM, it can be seen that the net events prevented remained positive (hence, a net public health benefit) at $\leq$80% to 90% diversion rates from the higher risk subgroup (Figure 2). At rates of diversion as observed in CUSTOM, the net public health benefit remained substantial.

A sensitivity analysis of the interaction between the percentage of the user population consisting of higher risk consumers and the total diversion rate from the higher risk subset was performed (Table 3). For these analyses, the non–higher risk consumers were assumed to have the same 10-year CHD risk as was observed in CUSTOM (estimated as 8% on the basis of the weighted distribution). Similarly, the higher risk subset was assumed to have a 10-year risk of 28%, as was approximated in CUSTOM (on the basis of the weighted distribution). Varying the contribution of the higher risk subset to the total cohort and the associated diversion rate in either direction from the CUSTOM population data still yielded substantial net event prevention in the setting of OTC lovastatin availability. Eliminating the CUSTOM users with a 10-year risk of $<$5% from the OTC user cohort further enhanced the public health impact per OTC user.

Potential secondary positive public health impact of OTC statins: The availability of an OTC statin, as well as the associated label materials and advertising, may help guide consumers to seek supervised lipid-lowering therapies. Large numbers of CUSTOM participants contacted healthcare professionals at varying points during the trial.[8,20] For example, of the 2,175 participants who reviewed the lovastatin OTC materials but did not use the drug, 503 discussed the OTC statin with their physician. Any initiation of lipid-lowering therapy as a result of these interactions would represent a public health benefit in addition to those observed in the OTC lovastatin users.

Focusing on the higher risk consumers who used OTC lovastatin in CUSTOM, many may have obtained supervised therapy during or after the study. For example, 9% of the higher risk cohort reported discussing their lipid therapy with their physician during the trial. Upgrading of therapy from OTC self-management to optimal, supervised therapy would add to the number of prevented events. An upgrade rate of 1 consumer for every 10 using the OTC statin would prevent 1,200 events in addition to those directly attributable to OTC statin use.

Discussion

The present analyses have made clear the importance of optimizing label communications so that use of an OTC statin by very low risk and higher risk consumers is minimized. Although on the whole, the CUSTOM cohort had a median absolute risk of approximately 10%, consistent with a moderate risk group, this was heavily influenced by the extremes of the distribution (Figure 1). Narrowing the risk distribution while maintaining the overall absolute risk would improve the overall public health benefit by minimizing the diversion from optimal care (Table 3).

Regardless of the magnitude of the potential public health benefit associated with OTC statin availability, patient risk and benefit is central to the therapeutic decision-making process. Because of the heterogeneity likely in an OTC population, as evidenced in CUSTOM, the patient benefit will vary widely and the direct risks and costs assumed will be similar. It is, therefore, critical that any OTC labeling effectively communicate a consumer's risks and expected benefits to facilitate informed decision making. Innovative shelf-based methods and postpurchase programs should allow patient risk profiles to be determined and communicated in meaningful terms to the consumer.

OTC statin accessibility alone clearly will not solve the problem of optimizing treatment of hypercholesterolemia in the general population, and serious questions must be addressed before an overall risk/benefit assessment can be made for OTC statin availability. An OTC statin will not be appropriate for many consumers, and product labeling and retail costs will prevent many of these consumers from using the drug. Nonetheless, for a subset of the currently untreated at-risk population, the present analyses provide a strong basis for expecting that an OTC statin option will reduce CHD risk with a clinically relevant net cardiovascular public health benefit.

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Appendix 10

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ORIGINAL RESEARCH ARTICLE

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Should We Encourage Over-The-Counter Statins?

A Population Perspective for Coronary Heart Disease Prevention

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Abstract

Background: Prescribed statin therapy has contributed to a dramatic reduction in primary and secondary coronary heart disease (CHD). In the UK, simvastatin is currently available without prescription; however, the US FDA rejected an application for nonprescription lovastatin in 2005.

Objective and methods: We used population impact measures for three hypothetical levels of CHD risk to estimate the number of CHD events that would be prevented in the US over 5 years under three scenarios: (i) prescription-only regulations; (ii) approval of over-the-counter (OTC) statins; and (iii) implementation of lifestyle interventions.

Results: For people at very low risk of CHD, 429 299 CHD events could be prevented by the availability of OTC statins and 560 243 CHD events could be prevented among this group by implementing lifestyle interventions. For those at moderate risk of CHD, 244 388 CHD events could be prevented by OTC statins compared with 318 866 by lifestyle interventions. For people at high risk of CHD, prescription statins could prevent 374 897 CHD events over the next 5 years.

Conclusions: Provision of OTC statins to US adults at low or moderate risk of CHD would have a greater impact on CHD prevention than providing prescription statins for those at high risk of CHD. Provision of OTC statins alongside lifestyle interventions among those at low or moderate risk of CHD could substantially reduce the number of CHD events in the population.

Prescribed statin therapy has contributed to a dramatic reduction in primary and secondary coronary heart disease (CHD).[1-3] The AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) demonstrated that treatment of middle-aged American men and women, with average levels of low-density lipoprotein-cholesterol (LDL-C), with lovastatin 20–40 mg/day yielded a reduction of 37% in CHD events.[2] In the US in 2005, an application to the US FDA by a pharmaceutical company to allow the public to purchase without prescription (over-the-counter [OTC]) lovastatin 20mg for CHD prevention was rejected[4] In the UK, simvastatin 10mg is available for purchase without prescription.[5]

It is difficult to assess the likely impact on population health of making low-dose statins available OTC without information on absolute numbers affected, and comparisons with other interventions (including doing nothing). Traditional measures of assessing population risk, such as the relative risk reduction and number needed to treat, do not account for baseline risk and cannot produce an estimate of the actual number of people affected.[6] Population impact measures (PIMs) can help to estimate the population impact of health interventions. PIMs provide a population focus to the interpretation of the results of observational studies and randomized controlled trials[6,7] and provide a population perspective to evidence-based practice.[8] The primary aim of PIMs is to provide information to policy makers about the expected impact of a course of action (or inaction) in terms of the number of people affected in the population they provide for.

In this article, we use population impact measures to estimate the impact on CHD events if OTC statins were approved, using three different assumptions of CHD risk in the general population. These findings were compared with the population impact of lifestyle interventions for those at low and moderate risk and with prescribing statins for people at high risk of CHD.

Methods

Data from the National Health and Nutrition Examination Surveys[9] was used to provide the numbers at risk of CHD in three different risk categories; low (<10%), moderate (10–20%), and high (>20%). Risk was based on the National Cholesterol Education Program–Adult Treatment Panel III risk score,[10] which is a modification of the algorithm from the Framingham Heart study[11] and includes the patient's age, total cholesterol concentration, smoking status, and SBP. Patients with CHD are considered to be at very high risk. The effectiveness of statin therapy among those at low or moderate risk of CHD,[2] the effectiveness of individual lifestyle interventions among those at low or moderate risk of CHD,[12] and the effectiveness of statin therapy among those at high risk of CHD events[1] were obtained from published literature. The effectiveness of lifestyle interventions was obtained from a systematic review[12] of multifactorial lifestyle-based interventions. For each baseline risk, we obtained the proportion of patients at risk who would take up the intervention[13-15] and the proportion who would persist with the intervention.[15-17] We obtained an estimate of the US population ≥25 years of age from the Centers for Disease Control and Prevention website.[18] We estimated the number of events prevented in the population (NEPP)[7] by the intervention (equation 1). All estimates are based on the impact of the intervention over a period of just over 5 years. The NEPP is calculated as (equation 1):

$$NEPP = N * r * P_d * P_e * P_a * RRR \quad \text{(Eq. 1)}$$

where N is the population size, r is the baseline risk, P_d is the prevalence condition in the population i.e. the proportion at risk, P_e is the proportion of those with the condition who are eligible for (or likely to take up) the intervention, P_a is the proportion of those with the condition who adhere to or persist with the intervention, and RRR is the relative risk reduction associated with the intervention.

The estimates of uptake and persistence used in the analysis were derived from the available literature[14-17,19] and we have performed a sensitivity analysis to determine the population impact of OTC statins and lifestyle advice if uptake and persistence were lower by 10 percentage points and higher by 10 percentage points, respectively.

Results

Among those with low baseline risk (5%), 326 227 CHD events would be prevented among the whole US adult population if OTC statins were available, compared with 425 733 if lifestyle-based interventions were offered to this population. Assuming a moderate baseline risk (15% risk in 10 years) 185 674 CHD events would be prevented among whole US adult population if low dose OTC statins were available compared with 242 308 for lifestyle-based interventions. Prescription statins for people at high risk (25% over 10 years) would prevent 237 406 CHD events among the whole US adult population (table I).

Thus, at a population level, the number of CHD events that would be prevented by OTC statins is around three-quarters of the number that would be prevented by lifestyle interventions. Furthermore, OTC statins would actually have a greater impact than the current strategy of prescription statins for those at high risk of developing CHD. However, OTC statins may be less effective from a population perspective among patients with a moderate risk (15% in 10 years) for CHD events.

The sensitivity analysis demonstrates that if we reduce the percentage of patients who take OTC statins to 10% and reduce persistence to 46% we can still expect to prevent 133 986 CHD events among those at low risk and 76 259 events among those at moderate risk.

Discussion

The evidence suggests that making low-dose statins available OTC to adults with low risk of CHD would have a greater impact in reducing CHD events than restricting them to patients at high risk of CHD. The population impact among those at low risk would be lower than implementation of lifestyle inventions among this group.

The rate of uptake of OTC statins is likely to be low, around 20%, whereas the uptake of lifestyle interventions is likely to be higher, around 52%. We have no estimate of the proportion of the population who, given either option, would both improve their lifestyle and purchase OTC statins. Therefore, we cannot estimate the potential overlap in terms of CHD events prevented by these two different strategies for people at low or moderate risk; however, the number of CHD events could be substantially reduced if OTC statins were available alongside interventions aimed at improving lifestyle. OTC statins are more likely to be purchased by consumers with knowledge of their lipid status[16] and this may suggest that OTC statins are more likely to be purchased by the 'worried well' or by more informed sections of the community. Nonetheless, the potential impact of OTC statins on the number of CHD events prevented will remain a fact.

The impact of OTC statins as proposed in the application by a pharmaceutical company to FDA may be slightly lower than we have estimated here. Our estimates were based on the results from the TexCAPS study that used lovastatin 20–40 mg/day, whereas

Table I. The number of coronary heart disease (CHD) events prevented in the US over a 5-year period by over-the-counter (OTC) statins and lifestyle changes

10-year baseline risk (%)	Intervention	Proportion of people at risk[9]	Proportion of patients who would take up the intervention[14,15,19]	Proportion of patients who persist with the intervention[15-17]	Relative risk reduction[1,12,13]	Number of CHD events prevented in the US (uptake and persistence ± 10%)
5	OTC statins	0.817	0.20	0.56	0.37	326 227 (133 986, 576 724)
5	Lifestyle	0.817	0.52	0.65	0.16	425 733 (290 960, 585 698)
15	OTC statins	0.155	0.20	0.56	0.37	185 674 (76 259, 328 245)
15	Lifestyle	0.155	0.52	0.65	0.16	242 308 (165 601, 333 353)
25	Prescription statins	0.029	0.80	0.59	0.36	237 406 (172 522, 312 349)

the dosage of lovastatin in the application to the FDA was 20 mg/day. However, other studies that discussed prevention among high-risk groups and primary prevention in Europe[20] and Japan[21] have demonstrated similar reductions in CHD events of 36% with very low-dose atorvastatin (10 mg/day) and 33% with low-dose pravastatin (10–20 mg/day).[14]

Adverse events associated with statin therapy occur in around 0.5% of people.[22] If low-dose OTC statin therapy is introduced in the USA, based on the estimates of uptake and persistence shown in table I we estimate that 100 701 people will experience a minor adverse event such as mylagia, myopathy, CKP elevations, or liver function test elevations that will subside when statins are discontinued (based on a rate of 0.5% among those audits in the US that take up the option of OTC statins and persist with using them). A further 2098 people will experience a serious adverse event such as rhabdomyolysis. The risk of a serious adverse event such as the potentially fatal condition of rhabdomyolysis is around 1 in 30 000–100 000 patient-years of exposure.[23] There may be an increased risk of adverse events among elderly people who are taking many other medications concomitantly, but this risk could be reduced by providing statins not 'over' the counter but from 'behind' the counter by knowledgeable pharmacy staff, as implemented in the UK.[24,25]

This method of calculation of the potential impact of an intervention on a population depends on the quality of the underlying data sources used in the calculations. Where possible, we have tried to use consistent definitions and systematic reviews or meta-analysis; however, data on uptake and persistence are not easily available.

This article highlights the need to take a population perspective based on absolute numbers when evaluating the potential impact of health interventions. The absence of good economic evaluations alongside epidemiologic studies means that it is difficult to incorporate additional information on costs into this type of population impact study. However, this article outlines the benefit of using a population-based approach when evaluating the potential impact of a proposed intervention such as OTC statins.

Conclusion

Statins are one of the cheapest and safest drugs known to effectively reduce CHD. Statin therapy has been shown to reduce CHD event rates by 37% among low- and moderate-risk groups. A recent meta-analysis demonstrated that the rate of serious adverse events was similar between statin and placebo recipients.[22] We have used a population-based approach to assess the potential impact of OTC statins on CHD events and have demonstrated that restricting access to OTC statins might not be in the public's interest and deserves more serious attention.

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