

Non-prescription Mevacor® 20 mg Joint Advisory Committee Meeting

NDA #: 21-213

Sponsor: Merck and Company
Johnson & Johnson Merck Consumer
Pharmaceuticals Co.

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I. BACKGROUND

I. A. History of Nonprescription Treatment of Hypercholesterolemia

Over-the-counter (OTC) management of hypercholesterolemia to reduce cardiovascular risk was first proposed in the mid-1990s, in applications to switch bile-acid binding resins from prescription-only to OTC dispensing. Advisory committee meetings were held in 1995 and again in 1997. No approvals were granted. As a result of the recommendations made by the Advisory Committees, the FDA issued a Guidance to Industry on Over-the-Counter Treatment of Hypercholesterolemia in 1997 (see attachment 1). In this document, hypercholesterolemia, a chronic, asymptomatic, metabolic derangement of multiple primary etiologies, was deemed a condition that required both accurate diagnosis, risk assessment, and, potentially, clinical testing as part of long-term follow up in the prevention of atherosclerotic cardiovascular disease. It was concluded that the medical management of this condition should be under the direction of a healthcare professional. This conclusion, therefore, precluded consideration of lipid-altering drugs as nonprescription drug products.

In July 2000, separate joint advisory committee meetings were held to discuss applications for the prescription to non-prescription (Rx-to-OTC) switches of two statins, lovastatin and pravastatin. Both sponsoring companies proposed a single, fixed dose of 10 mg as safe and effective for patients without clinically evident heart disease but who were at risk because of mildly elevated Total-C (200-240 mg/dL) and LDL-C (> 130 mg/dL). The Advisory Committee members recommended that both applications not be approved based on concerns of inadequate effectiveness (lipid altering and thus CV risk reduction) of the products and about safe and appropriate self-management of hypercholesterolemia given the data suggesting poor consumer comprehension of labeling.

In October 2000, the FDA took a "Not Approved" action on Merck's application, stating that *"neither the rationale for treating the proposed target population with Mevacor 10 mg in the over-the-counter (OTC) setting, nor a favorable benefit/risk ratio for such treatment has been adequately established. Furthermore, the ability of consumers to appropriately self-select and to adequately comply with chronic Mevacor therapy without the intervention of a physician has not been demonstrated"*.

Specific deficiencies of the application were also outlined in the letter and can be briefly summarized as follows:

- Current National Cholesterol Education Program (NCEP) Guidelines were not incorporated in the OTC treatment paradigm
- Inadequate information was provided, specifically regarding the Mevacor 10 mg dose and the proposed OTC target population, to support an expectation of a clinical benefit for Mevacor based on extrapolation from the clinical outcomes study, Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)
- The OTC study program had not included a cholesterol treatment goal, did not evaluate whether consumers would comprehend the importance of a treatment goal, and did not address whether consumers would make appropriate decisions in the event of not achieving that treatment goal
- The clinical and actual use studies failed to demonstrate that consumers understood the complexities of treating a chronic medical condition such as hypercholesterolemia. Specifically, assessment of individual CV risk, compliance, and adherence to chronic lovastatin therapy were deficiencies noted in the review of these trials.

- The program did not explain how a consumer can use an over-the-counter product whose prescription label recommends hepatic transaminase monitoring. In addition, the program did not demonstrate an ability of consumers to comprehend the risk of serious muscle toxicity associated with Mevacor therapy.
- Lovastatin is extensively metabolized by cytochrome P450 3A4 and many drugs may interfere with the metabolism of Mevacor OTC which would increase the risk for serious muscle toxicity. The OTC program did not demonstrate that consumers would understand the importance of drug-drug interactions.
- Post-approval consumer education programs and materials were not adequately tested. Information on the availability of accurate cholesterol testing in the OTC setting to allow informed selection and monitoring of therapy by consumers was not adequately provided in the NDA.
- Lovastatin is labeled Pregnancy Category X (not to be used in pregnancy). Given that Mevacor OTC was likewise proposed to be contraindicated in pregnancy, label comprehension in this regard as well as the actual potential of such use was not assessed. Additional postnatal development studies in animals (modeling human fetal neurological development) were recommended to shed further light on risks to the fetus of *in utero* lovastatin exposure.

Despite the non-approval recommendation, the Agency recognized that public interest in the availability of safe and effective therapies to treat hypercholesterolemia warranted interactions between Industry and the Agency to evaluate the feasibility of such therapies as nonprescription products. In order to formally re-open such discussion, in 2001, the Agency withdrew the 1997 Guidance to Industry. Over the past four years, meetings and formal and informal communication have occurred between members of the Division of Metabolic and Endocrine Drug Products (DMEDP) and Division of Over-the-Counter Drug Products (DOTCDP) and representatives of Merck

I. B. New Guidelines for the Management of Hypercholesterolemia

Shortly after the action letter for NDA 21-213 was issued, the National Cholesterol Education Program (NCEP) published its third Executive Summary on the management of hyperlipidemia in adults (Adult Treatment Panel III or ATP III).¹ (see attachment 3) and promulgated new treatment guidelines. While a detailed discussion of these recommendations is beyond the scope of this briefing document, several new features of the NCEP Guidelines are relevant to the review of RX-to-OTC lovastatin switch.

Under ATP-III, treatment approaches, decisions on initiating drug therapy, and goals of therapy are based on calculations of an individual's risk of experiencing a CV event over a 10-year period. ATP-III uses Framingham point scores in estimating these 10-year CHD risks, with age, total-C, smoking status, HDL-C, and blood pressure contributing to the total score. These 10-yr CHD risk estimates determine whether an individual falls into one of 4 categories:

- CHD or CHD risk equivalents (10-yr risk > 20%)
- 2+ risk factors for heart disease (10-yr risk 10-20%)
- 2+ risk factors for heart disease (10-yr risk < 10%)

¹ 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). *JAMA*. 2001; 285(19):2486-2497.

- none to 1 risk factor for heart disease

Individuals with diabetes but without clinically evident CHD and those with other clinical forms of atherosclerotic disease (e.g., peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease) have equivalent status to those individuals with established CHD. Risk factors for heart disease that may modify LDL-C goals include smoking, HTN, HDL < 40 mg/dL, family history of premature CHD, and age.

While an over-simplification of the NCEP ATP-III publication, the following table summarizes the treatment approach for hypercholesterolemia.

Table 1. LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories as Summarized in the 2001 NCEP Guidelines for the Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Risk Category	LDL Goal (mg/dL)	LDL Level at which to initiate TLC (mg/dL)	LDL-C level at which to consider drug therapy (mg/dL)
CHD or CHD risk* equivalents (10-yr risk > 20%)	< 100	≥ 100	≥ 130 (100-129; drug optional)
2+ risk factors (10-yr risk ≤ 20%)	< 130	≥ 130	10-yr risk 10-20%: ≥ 130
	< 130	≥ 130	10-yr risk <10%: ≥ 160
0-1 risk factor (10-yr risk < 10%)	160	≥ 160	≥ 190 (160-189:LDL-lowering drug optional)

*recent clinical trial data have resulted in recommendations for more aggressive LDL-lowering to < 70 mg/dL for patients at very high risk for a CV event

The NCEP ATP-III Guidelines also identified other lipid parameters beyond LDL-C that contributed to the atherosclerotic process that required treatment intervention if abnormal. Specifically, elevated serum triglyceride (TG) levels may contribute to risk for CHD, and the optimal level should be < 150 mg/dL. In patients who have reached their LDL-C goal but whose TGs were > 200 mg/dL, a secondary target of therapy is non-HDL-C (this comprises the pool of atherogenic, cholesterol-ester containing, apo B lipoproteins) with the goal being set 30 mg/dL higher than that for LDL-C. In many instances, this secondary target of therapy must be addressed with additional lipid-altering therapies (e.g., fibrates, niacin). Table 2 summarizes LDL-C and non-HDL-C goals of therapy by risk category.

Table 2. LDL-C and Non-HDL-C Goals for the 3 Risk Categories based on NCEP ATP-III

Risk Category	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
CHD and CHD risk equivalent	< 100	< 130
2+ risk factors	< 130	< 160
0-1 risk factor	< 160	< 190

In July 2004, members of the Coordinating Committee of the National Cholesterol Education Program published updates to NCEP ATP-III based on the results of 5 major clinical outcomes trials published after May 2001.² (see attachment 4) These revised recommendations stated that in individuals with very high risk for a CV event, an LDL-C goal of < 70 mg/dL is a therapeutic option.

Based on these NCEP Guidelines and their recent updates, it is evident that the treatment approach for elevated cholesterol levels is complex, requiring more than just knowing one's cholesterol level. It should be anticipated that as additional data are available from clinical trials, as new information on risk factors and risk-factor management emerges, and as new therapeutic alternatives come to the fore, treatment recommendations are more than likely to be modified. Furthermore, the extent to which a given, single-drug, fixed-dose OTC treatment model adequately addresses current clinical goals of and/or can be adapted to this complex and changing area of medical management must be carefully considered.

II. PROPOSED OTC-ELIGIBLE PATIENT POPULATION AND LOVASATIN DOSE

The applicant identified the OTC-eligible population as being:

“a primary prevention population with ≥ 2 risk factors and a $\leq 20\%$ risk of CHD over 10 years without underlying chronic conditions that complicate consumer self-management.”

The applicant further states that individuals with liver disease, LDL-C > 170 mg/dL, the metabolic syndrome, diabetes, CHD, a history of stroke or other atherosclerotic cardiac disease are not candidates for OTC lovastatin. These patients were excluded from nonprescription lovastatin use because their 10-yr CHD risk would unlikely be adequately treated with lovastatin 20 mg and more aggressive management of other risk factors would require direct physician management.

Consumers are considered eligible for nonprescription lovastatin if they meet the following criteria on the product label:

1. males 45 yrs or older or females 55 years or older; and
2. LDL-C between 130 and 170 mg/dL; and
3. having at least one of the following risk factors
 - smoking

² Grundy SM et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004; 110:227-239.

- HDL-C between 1 and 39 mg/dL
- family history of heart attack in father/brother before age 55 or mother/sister before age 65
- high blood pressure

The Mevacor OTC-eligible patient population therefore corresponds with those individuals who are at intermediate risk for a CV event over 10 years (highlighted yellow in Table 1). Based on NCEP ATP III guidelines, LDL-C goal for the OTC-eligible population is < 130 mg/dL. Drug therapy should be considered after therapeutic lifestyle changes fail to achieve this goal (or < 160 mg/dL if 10-yr risk is < 10%).

In the original NDA submission for nonprescription lovastatin, the applicant proposed to market the 10 mg dose for OTC use. This dose was studied in a clinical efficacy study in the initial NDA submission and an average LDL-C reduction of 18% was observed in a population with a mean LDL-C of 143 mg/dL. Consequently, the LDL-lowering efficacy at this dose was thought to be inadequate for the current proposed OTC population. Furthermore, no data on clinical benefit were available at that dose.

In this resubmission, the sponsor has proposed a fixed daily dose of lovastatin 20 mg for nonprescription use.

III. CLINICAL DATA SUBMITTED IN SUPPORT OF NDA

The only new studies conducted for this NDA resubmission were a label comprehension study and a consumer use study. The label comprehension study was conducted after a series of pilot studies was conducted. The label that was evaluated in the label comprehension study was also studied in the consumer use study, Protocol 084 (CUSTOM), which was in progress when the label comprehension study began. Both of these studies were reviewed in detail by the Division of Over-the-Counter Drug Products with separate reviews provided in this briefing document.

The applicant has also summarized data from studies submitted to the NDA for prescription lovastatin and studies previously reviewed under the original NDA submission for non-prescription lovastatin 10 mg. In addition, worldwide marketing safety data and selected reviews of published literature on lovastatin are provided with this submission.

III. A. Efficacy Data

A significant portion of the efficacy data for nonprescription lovastatin relies on 2 controlled studies: the Expanded Clinical Experience with Lovastatin (EXCEL) and Air Force/Texas Coronary Atherosclerosis Project (AFCAPS/TexCAPS). These studies were submitted and reviewed as efficacy supplements to the prescription NDA and their data are already in the product label. This briefing document will only highlight the efficacy findings from these two studies and comment on what relevance they have for nonprescription lovastatin use.

III. B. Safety Data

The safety concerns associated with lovastatin that were outlined in the non-approval letter included muscle toxicity with drug-drug interactions representing an increased risk for muscle toxicity, increases in hepatic transaminases and Rx recommendations for clinical laboratory monitoring, and pregnancy category X labeling. The applicant has addressed two of these safety concerns by submitting data to the prescription NDA.

Preclinical/reproductive and toxicology data were submitted under supplement 061 to NDA 19-643 and reviewed by Dr. Karen Davis-Bruno. Her review of the data and the Agency's recommendation on pregnancy category X labeling are discussed in separate documents included in this briefing package.

In view of the minimal benefit of continued use of lovastatin therapy during pregnancy, and the applicant's intention to maintain a contraindication for use during pregnancy, the prescription product label will retain its Pregnancy Category X labeling. For purposes of nonprescription lovastatin use, the Agency noted that OTC labels do not currently have a pregnancy category designation but carry language that would advise women on the safe use or avoidance of the product during pregnancy. As prescription labeling for lovastatin will remain Pregnancy Category X and contraindicated in pregnant women, the safety of nonprescription lovastatin would require the demonstration that females of childbearing potential or who are pregnant comprehend the product label and appropriately select or de-select to avoid any risk to the fetus.

The second safety concern that was addressed as a supplement to the prescription NDA was hepatic enzyme elevations and recommendations in the prescription labeling that patients have baseline and periodic monitoring of hepatic transaminases while taking lovastatin. No new studies were conducted by the applicant to support changes to the prescription labeling. However, the applicant referenced safety data from EXCEL, AFCAPS/TexCAPS, the Heart Protection Study which evaluated a similar HMG-CoA reductase inhibitor (simvastatin), worldwide safety reports, and published literature. This supplement was submitted to the Agency in July 2004 and is currently under review; however, this briefing document will provide an overview of the applicant's rationale for relying on these data to modify recommendations to the prescription labeling.

IV. CLINICAL EFFICACY

IV. A. Lipid-Altering Efficacy

Lipid-altering efficacy of lovastatin 20 mg is summarized from 3 different clinical sources: EXCEL, AFCAPS/TexCAPS, and CUSTOM. These three studies involved different patient populations, study designs, and treatment approaches. Consequently, differences in efficacy are not unexpected. The following table highlights relevant baseline features of the three study cohorts.

Table 3. Selected Baseline Characteristics of EXCEL, AFCAPS/TexCAPS and CUSTOM Cohorts

	EXCEL N=8245	AFCAPS/TexCAPS N=6605	CUSTOM N=1061
Gender			
male	4855 (58.9%)	5608 (84.9%)	631 (59.5%)
female	3390 (41.1%)	997 (15.1%)	430 (40.5%)
Age, yrs			
mean ± SD	male 53.9 ± 10.4 female 58.4 ± 7.8	all 58 ± 7	all 56.5 ± 11.03

range	21-75	45-73	23-87 female 23-86
Mean Lipid Profile, mg/dL			
LDL	180 ± 20.7	150.4 ± 16.8	157.3 ± 41.8 (n=931)
TC	258.1 ± 20.5	220.8 ± 20.9	246.1 ± 48.2 (n=1053)
HDL	45 ± 12.1	37.0 ± 5.6	47.0 ± 13.5 (n=1014)
TG	154 (median)	168.1 ± 64.1	225.4 ± 136.5 (n=1052)*

The EXCEL cohort included patients with higher baseline cholesterol levels than AFCAPS/TexCAPS and CUSTOM. Lipid values in CUSTOM were obtained on fasting or non-fasting samples whereas the controlled clinical studies required overnight fasting. Elevated mean TG levels in the CUSTOM cohort likely reflect this difference in biochemical testing. An analysis of baseline TG levels in the CUSTOM trial by fasting vs non-fasting sample does reveal a lower mean TG value for the fasting population (203.2 ± 126.4 mg/dL).

EXCEL

EXCEL was a randomized, double-blind, placebo-controlled study evaluating 5 treatment groups: lovastatin 20 mg q pm; lovastatin 40 mg q pm; lovastatin 20 mg bid; lovastatin 40 mg bid; and placebo. There were 1,642 patients randomized to the lovastatin 20 mg daily group. A 4- to 6- week diet-only, run-in, baseline period was followed by a 48-week diet and active treatment period. The primary efficacy endpoints were the proportion of patients achieving specific lipid goals at Week 48 of TC < 200 and < 240 and LDL < 130 and 160. Mean percentage change from baseline at Week 48 was also calculated.

By Week 48, 31% of the lovastatin 20 mg daily treatment group had achieved an LDL-C < 130 mg/dL and the mean percent change from baseline was -24%. Mean changes for HDL-C and TG levels were +6.6% and -6.0%, respectively.

AFCAPS/TexCAPS

AFCAPS/TexCAPS randomized 6,605 patients to lovastatin 20 mg daily (n=3304) or placebo (n=3301). Lovastatin dose was titrated to 40 mg daily if at Week 18, LDL-C levels remained > 110 mg/dL. Approximately half of the lovastatin-treatment group were titrated to the 40 mg dose. The applicant presented data at Week 18 which represented only lipid-altering efficacy at the 20 mg daily dose. These data were available from only one of two sites which analyzed lipids during this clinical trial. Lipid-altering data at 1 year in only those patients remaining on the lovastatin 20 mg dose were also evaluated. The mean percent change in LDL-C from baseline in both analyses was approximately -24.0%. The applicant also presented the percent of patients reaching an LDL-C goal of < 130 mg/dL at Week 18. In these patients, 85.8% achieved and LDL-C goal of < 130 mg/dL.

Reviewer Comments:

Based on two large, placebo-controlled clinical trials evaluating lipid-altering efficacy of lovastatin, the expected mean reduction in LDL-C associated with the lovastatin 20 mg dose is 24%. The applicant has also summarized the proportion of patients in each of the two cohorts who achieved an LDL-C < 130 mg/dL while on lovastatin 20 mg. This analysis is intended to provide some estimate of the effectiveness of the nonprescription

product achieving NCEP-ATP III goals for the targeted OTC population. Only 31% of patients on lovastatin 20 mg in EXCEL achieved an LDL-C goal of < 130 mg/dL; however, this study enrolled patients with higher baseline cholesterol levels. As the mean LDL-C level was about 30 mg/dL higher in EXCEL compared to AFCAPS/TexCAPS and CUSTOM (see Table 3), it is not unexpected that a smaller percentage of this cohort would achieve the fixed target goal of < 130 mg/dL.

In contrast, the applicant summarized that by Week 18, 85.8% of the AFCAP/TexCAPS cohort who were OTC-eligible achieved an LDL-C goal of < 130 mg/dL. A similar analysis was performed by Week 6, a timepoint at which consumers are advised to get cholesterol testing if using OTC lovastatin. By Week 6, 86.2% of the AFCAPS/TexCAPS OTC-eligible population achieved an LDL-C goal of < 130 mg/dL with lovastatin 20 mg daily. It should be noted that during the conduct of AFCAP/TexCAPS, the two analytical labs performing lipid measures changed methods of analyses mid-study. Consequently, the proportion of OTC-eligible patients in AFCAPS/TexCAPS is summarized for only those patients with pre- and post-values using the same method (approximately two-thirds of the cohort).

In conclusion, in controlled clinical trials where patients enter dietary run-in periods, are selected by clinical investigators based on inclusion/exclusion criteria, and receive recommendations for dietary and lifestyle interventions, lovastatin 20 mg daily treatment results in mean reductions in LDL-C of 24%. Data from the AFCAPS/TexCAPS trial suggest that a significant proportion of patients who are OTC-eligible can achieve an LDL-C goal of < 130 mg/dL with lovastatin 20 mg. However, these data are based on an analysis after 6 and 18 weeks of therapy and data on long-term maintenance of this goal in a non-prescription setting are not available.

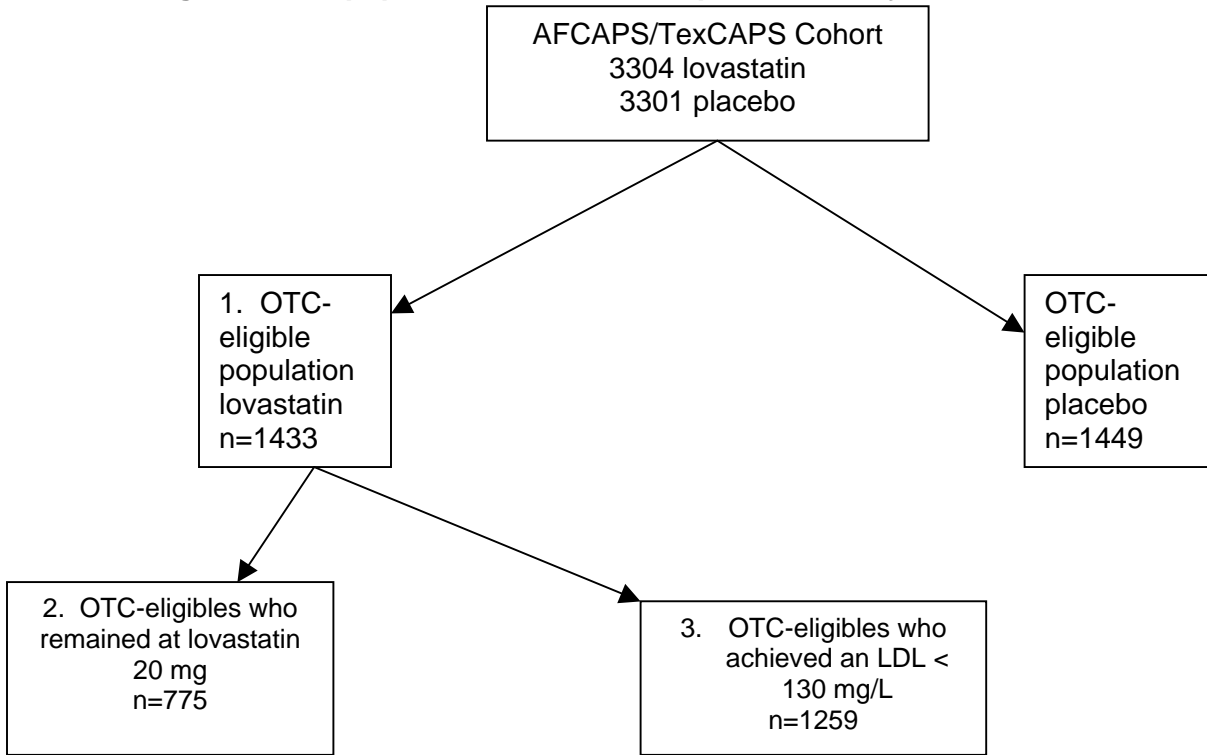
IV. B. Clinical Benefit

Elevated cholesterol level is an established risk factor for cardiovascular disease and its reduction has been shown in multiple clinical studies to reduce the risk of experiencing a CV event. Lovastatin is among several statins that have been proven to reduce CV event rates based on data from large, placebo-controlled clinical outcomes trials. For lovastatin specifically, that trial is AFCAPS/TexCAPS.

AFCAPS/TexCAPS was a 5-year, randomized, double-blind, placebo-controlled clinical outcomes study that evaluated the effects of lovastatin 20 to 40 mg daily on reducing the risk of one or more manifestations of atherosclerotic vascular disease. The primary endpoint of the study was a composite of unstable angina, fatal or non-fatal MI, or sudden death. Patients were randomized to placebo or lovastatin 20 mg and at Week 18, if LDL-C remained > 110 mg/dL, the lovastatin dose was increased to 40 mg with a randomly selected placebo patient matched for upward titration. Although a primary prevention study in individuals that might be considered at average risk for heart disease, this trial selected certain characteristics that marked relatively high short-term risk of heart disease. These characteristics included age (males \geq 45 yrs and females \geq 55 yrs) and a low HDL-C (males had to have HDL < 45 mg/dL and females < 47 mg/dL). Patients also had to have a Total-C/HDL ratio of > 6.0 if LDL-C was between 125 and 129 mg/dL. After an average follow-up period of 4.6 years, lovastatin 20 to 40 mg reduced the risk of experiencing a primary endpoint by 37% ($p < 0.0001$) with 116 events (3.5%) occurring in the lovastatin group compared to 183 events (5.5%) in the placebo group.

A post-hoc analysis of the AFCAPS/TexCAPS database was undertaken by the applicant wherein three sub-populations were evaluated. These sub-populations can be described as follows:

Figure 1. Subpopulations evaluated in post-hoc analysis of clinical benefit



Subpopulation 1 was comprised of individuals in the AFCAPS/TexCAPS cohort who would have met the inclusion/exclusion criteria for Mevacor OTC use. Both the lovastatin and placebo groups were selected from the randomized cohort.

Subpopulations 2 and 3 are selected from Subpopulation 1. Subpopulation 2 would include only those patients from the lovastatin-treatment group who remained on 20 mg throughout the clinical trial. (i.e., those patients at Week 18 whose LDL-C were < 110 and did not require upward titration to 40 mg). Subpopulation 3 would include only those OTC-eligible patients from the lovastatin-treatment group who reached an LDL-C < 130 mg/dL at week 6.

Within each subgroup the applicant analyzed the observed event rate per 1000 patient-years at risk and the Kaplan-Meier event rates. For subpopulations 2 and 3, these event rates were also calculated for a matched control group. The following table derived from the applicant's submission summarizes these analyses and a calculated number needed to treat in each subpopulation.

Table 10.

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.						

Based on this post-hoc analysis, the applicant concluded that the lovastatin treatment subpopulations had a significantly lower risk of having a CHD event than their placebo counterparts.

Reviewer Comments:

The comparisons between lovastatin treatment and placebo in subpopulations 2 and 3 do not represent comparisons of two randomized treatment groups. While baseline characteristics may appear similar based on matching criteria, randomized comparison ensures that imbalances that are expected and unexpected between treatment groups are eliminated. This cannot be assumed for subpopulations 2 and 3.

Subpopulation 2 (non-titrators) isolated those patients in AFCAPS/TexCAPS who maintained therapy with the proposed nonprescription dose of lovastatin 20 mg. However, this group of patients represents individuals in AFCAPS/TexCAPS who were able to achieve an LDL-C goal of < 110 mg/dL by Week 18 with lovastatin 20 mg. In the actual use study, proportion of consumers achieving an LDL-C goal < 110 mg/dL was not evaluated; however, the applicant did summarize the number of patients who purchased and used Mevacor OTC who achieved an LDL-C of < 100. From Table D-38 of sponsor's submission, only 208/1059 (19.6%) achieved this goal. It is unlikely that a nonprescription lovastatin 20 mg fixed dose will be able to achieve the LDL-C target therapy of AFCAPS/TexCAPS that was associated with the 37% risk reduction in the clinical trial.

Subpopulation 3 (OTC-eligible patients achieving LDL goal < 130 mg/dL by week 6) includes patients who subsequently had to have their lovastatin dose increased to 40 mg daily because an LDL-C goal of < 110 mg/dL (per AFCAPS protocol) was not achieved. The nonprescription program does not include recommendations for upward titration nor does it recommend a similar treatment goal.

While it is logical to assume that an individual taking nonprescription lovastatin 20 mg and has some reduction in cholesterol levels will also lower his/her risk of heart disease, a numerical assignment of risk reduction based on AFCAPS/TexCAPS is not possible. The estimates of risk reduction in the Mevacor-OTC eligible patient population are based on analyses of subpopulations in AFCAPS/TexCAPS that had an average treatment follow-up period of 5 years. During this follow-up period, dietary reinforcement and other risk factor modifications were provided to study participants. Study visits occurred every 6 weeks for the first 48 weeks of the study and every 6 months thereafter. The true risk reduction for nonprescription lovastatin use must factor in effectiveness of therapy (i.e., adequate LDL-lowering), long-term adherence to therapy and therapeutic lifestyle interventions, and appropriate management of other CHD risk factors. To date, the Agency only has 6 months of data for Mevacor 20 mg in the proposed OTC population.

In sum, even if one accepts the post-hoc subgroup analyses from AFCAPS, the NNT calculations represent truly a “best case scenario” assessment of the population effects, and thus of the probability of individual benefit, in CV risk reduction of Mevacor 20 mg OTC. While perhaps only 28 people meeting eligibility criteria and responding with the expected degree of LDL reduction would have to take lovastatin 20 mg daily for an average of approximately 5 years to save one event, it seems clear that the NNT would rise rapidly as the time-integrated lipid-altering effectiveness of the treatment regimen was reduced. At this time, however, we have no information on CV risk reduction with short-term or occasional treatment with lovastatin 20 mg, which would seem likely to characterize a significant proportion of Mevacor OTC use.

A separate memo from FDA statistician, Joy Mele, MS, on this analysis is included in this briefing document.

V. CLINICAL SAFETY

V. A. Muscle-Related Safety

Muscle toxicity with rare cases of rhabdomyolysis has been reported for all marketed statins. Clinical presentations are variable and can range from mild muscle aches and pains to severe muscle cell breakdown with renal failure that may be fatal. In clinical trials, patients have been identified with very elevated creatine kinase levels (e.g., > 10,000) in the absence of clinical symptoms. Myopathy, which is defined as CK elevations > 10x ULN with muscle symptoms, is estimated to occur between 0.1 to 0.6% of patients evaluated in clinical trials of statins across all doses studied. The more severe form of muscle toxicity, rhabdomyolysis, occurs less frequently and is estimated to have an incidence of 0.03 to 0.05%.³

The incidence of myopathy by dose in EXCEL was 0%, 0.1%, and 0.2% in the 20 mg daily, 40 mg daily, and 80 mg daily doses, respectively. No cases of rhabdomyolysis associated with lovastatin occurred in EXCEL while one patient treated with lovastatin 20 mg developed rhabdomyolysis in AFCAPS/TexCAPS. This case occurred in a patient who had recently undergone prostate cancer surgery. In this same study, 2 patients randomized to placebo had also developed rhabdomyolysis.

The applicant performed a search of its worldwide safety database of postmarketing adverse experience reports. Preferred terms of myopathy, muscle disorder NOS (not otherwise specified), myopathy toxic, myositis, myositis-like syndrome, polymyositis,

³ Thompson PD et al. Statin-associated myopathy. *JAMA* 2003; 289(13):1681-1690.

rhabdomyolysis, myoglobin urine present, myoglobinuria, or blood myoglobin increased were selected. From approval (1987) until June 1, 2003, the applicant identified 874 reports containing one or more of the search terms. Based on an estimated worldwide exposure to lovastatin of approximately 27 million patient-treatment years, the applicant calculated a reporting rate of myopathy of approximately 3 per 100,000 patient years. Focusing only on reports of rhabdomyolysis, the applicant identified 334 reports representing a reporting rate of 1.2 per 100,000 patient-treatment years.

Evaluations of spontaneous adverse event reports for statin-associated muscle toxicity have also been performed by the FDA's Office of Drug Safety. From approval (1988) to July 2001, FDA reviewers retrieved 120 domestic cases of rhabdomyolysis in the Adverse Event Reporting System. Rhabdomyolysis was defined as CK > 10,000 IU/L with signs and symptoms and clinical diagnosis of rhabdomyolysis. Given the estimated numbers of prescriptions dispensed for lovastatin in the United States during this time period, the crude reporting rate of rhabdomyolysis per 100,000 prescriptions was 0.12.⁴ A more recent analysis of the prescription claims database from 11 geographically dispersed U.S. health plans during January 1, 1998 through June 30, 2001 revealed too low usage of lovastatin to provide updated risk assessments for rhabdomyolysis.

Based on clinical trial data and different analyses of postmarketing spontaneous adverse event reports, the incidence of myopathy and rhabdomyolysis associated with lovastatin use is a very rare event. Given the lipid-lowering effects and clinical outcome data for lovastatin, the risk of myopathy/rhabdomyolysis does not appear to outweigh the benefit of lovastatin therapy.

The main concern of myopathy risk in the nonprescription setting is whether consumer behavior would differ from that in prescription use which would result in more individuals experiencing muscle toxicity than if they were receiving lipid-altering therapy as a prescription product. In this matter, two points require further discussion.

Firstly, the risk of muscle toxicity for lovastatin can be increased when the drug is co-administered with a potent CYP3A4 inhibitor with increase in exposure to lovastatin, a drug that will otherwise increase lovastatin drug levels, or a drug with inherent myotoxic effects. The following table summarizes the change in lovastatin exposure levels when it is co-administered with certain drugs/food that affect its bioavailability or metabolic clearance. These data are derived from pK studies performed by the applicant or published studies.

Table 11. Effect of coadministration of CYP3A4 inhibitors and gemfibrozil on Lovastatin Levels

	Number of Subjects	Dosing of Co-administered Drug or Grapefruit Juice	Dosing of Lovastatin	AUC Ratio ¹ (with / without co-administered drug) No Effect = 1.00	
				Lovastatin	Lovastatin Acid
Erythromycin	12	500mg TID for 7 days	40mg QD for 7 days	5.7	N.A.
Gemfibrozil	11	600mg BID for 3 days	40mg (single dose)	0.96	2.8
Itraconazole	12	200mg QD for 4 days	40mg (single dose)	19	19
Grapefruit Juice (high dose)	10	200mL of double-strength [#]	80mg (single dose)	15	5

⁴ Chang et al. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepidemiology and Drug Safety* 2004; 13:417-426.

¹: results based on a chemical assay except one of results with grapefruit juice as indicated.

N.A.: not available

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

The applicant addresses this matter by including in the product label the recommendation that consumers ask their doctor or pharmacist before use if they are taking any prescription medicine or other cholesterol-lowering medicine, emphasizing that certain drugs can interact with lovastatin. The label also tells consumers to tell their doctor that they are taking nonprescription lovastatin before they start taking any new prescription medicine. As the list of interacting medications with lovastatin will increase over time (in the past 3 years verapamil, diltiazem, telithromycin, and danazol have been added to or are under negotiations for inclusion into the WARNINGS and PRECAUTIONS section of the label), the applicant is proposing that this labeling alerts consumers to consider every current and new drug as a potential interacting drug with lovastatin that would lead them to seek professional advice before taking or continuing lovastatin.

The second point for consideration is that the risk of muscle toxicity is increased with higher doses of statin. The dose proposed for nonprescription use has a modest effect on cholesterol-lowering compared to other approved statins, including those that are not CYP3A4 substrates. The potential of consumer upward titration of lovastatin to achieve recommended LDL-C treatment goals should be a consideration in evaluating the risks of muscle toxicity in the nonprescription setting.

V. B. Hepatic Safety

All statin labels were approved with recommendations for baseline and periodic post-baseline monitoring of hepatic transaminases. These recommendations arose from the observation that a slightly higher percentage of patients in controlled clinical trials developed transaminase elevations compared to placebo. However, these elevations rarely resulted in any serious clinical sequelae and rare postmarketing reports of hepatic failure are often complicated by other serious medical conditions and concomitant medical therapies such that attribution of event solely to lovastatin use is not possible.

The incidences of consecutive > 3x ULN increases in hepatic transaminases were evaluated in EXCEL and AFCAPS/TexCAPS. Both these studies excluded patients with baseline liver abnormalities. EXCEL excluded patients with any pre-existing elevation of liver transaminases while AFCAPS/TexCAPS excluded patients with hepatic transaminase elevations > 1.2 x ULN. The incidences of consecutive elevations >3x ULN in hepatic transaminases in both these studies are summarized in the following table:

Table 12. Frequency of Consecutive Liver Transaminase Elevations > 3x ULN in Clinical Trials

Consecutive > 3xULN elevations of ALT or AST	EXCEL					AFCAPS/TexCAPS	
	Lova 20 mg qd n=1642	Lova 40 mg qd n=1645	Lova 20 mg bid n=1646	Lova 40 mg bid n=1649	Pbo n=1663	Lova 20/40 mg n=3242	Pbo n=3248
	2 (0.1%)	12 (0.9%)	11 (0.9%)	20 (1.5%)	2 (0.1%)	18 (0.56%)	11 (0.34%)

Over the past 5+ years, several applications have been submitted to the FDA to reduce the recommendation for post-baseline monitoring of hepatic transaminases in different statin labels. Data from long-term, placebo-controlled studies strongly suggested that patients without clinical or laboratory evidence of liver disease could be safely treated with certain statins without monitoring of hepatic transaminase levels unless clinically indicated or if patients were treated with higher doses of the statin. Baseline monitoring is still recommended for all statins as no adequate data were available for patients with elevated hepatic transaminases or patients with chronic, asymptomatic liver disease (e.g., NASH or chronic hepatitis C). In short, while there seems little to no hepatic risk of statins in patients with normal hepatic function, the hepatic risks, if any, of statin therapy in patients with liver disease has not been studied. To the extent that much early liver disease is asymptomatic, this issue must be addressed in considering OTC availability of lovastatin.

The applicant had been informed in July 2002 that while data from controlled studies such as AFCAPS/TexCAPS and EXCEL might address the proposal to remove post-baseline monitoring of hepatic transaminase levels, these data would not remove recommendations for baseline testing as exclusion criteria of both these trials resulted in no safety data for those patients with chronic, asymptomatic liver disease who might be identified with a liver panel test.

In this resubmission the applicant references data submitted in a supplement to the prescription NDA that is currently under review. No new studies on the safety of lovastatin in patients with chronic liver disease were performed for this resubmission or the supplement to the prescription NDA. Testimonials from hepatologist consultants were recently submitted to the NDA to provide a rationale for not conducting prospective studies in patients with chronic, asymptomatic liver disease (see attachment x and x). The applicant has discussed in detail the findings from two studies submitted to both applications.

Study 1⁵ (see attachment x)

An abstract of a study conducted at the Weill Medical College of Cornell University was provided in this resubmission. The medical records of 14 patients who were started on a statin and whose liver profiles were available from baseline were reviewed. The liver profiles on 2 or more post-baseline assessments were also known in these subjects. These subjects comprised Group 1.

Retrospective data from 2 “control” groups were evaluated. Group 2 consisted of 14 patients with chronic hepatitis C who were on a statin and Group 3 consisted of 14 patients with hepatitis C virus who were not on a statin.

Lovastatin was not used by any subjects in the Groups 1-3. Statins used included atorvastatin, pravastatin, and simvastatin. The authors of this small study concluded the following:

- minor ALT and AST elevations are common in patients with chronic hepatitis C between 1 and 6 months after starting a statin and that none of the elevations resulted in changes in statin dose or discontinuation of medication

⁵ Ahmed F and Jacobson IM. Safety of statins in patients with chronic hepatitis C (abstract)

- patients with chronic hepatitis C who are on a statin have slightly higher ALT and AST values than those who are not on a statin
- statins seem to be safe in patients with chronic hepatitis C but further studies on a larger number of patients are warranted

Study 2⁶ (see attachment x)

In another retrospective study conducted by investigators at the Indiana University School of Medicine, 3 cohorts were evaluated to determine the safety of statins in patients with elevated transaminase levels. Cohort 1 consisted of hyperlipidemia 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. Patients with evidence of alcohol use, hepatitis B surface antigen, or hepatitis C antibody were excluded. Patients had to have had liver biochemistry results available from 6 months before and 6 months after starting a statin. Elevations in liver biochemistries were defined as mild to moderate or severe as follows:

- mild-to-moderate: elevations of AST and/or ALT *up to* 10 x ULN in patients with normal baseline enzymes or *up to* 10-fold elevations from their baseline values of AST and/or ALT in patients with elevated liver enzymes at baseline
- severe: the development of serum bilirubin > 3 mg/dL regardless of baseline transaminase values or elevations of AST and/or ALT *greater than* 10 x ULN in patients with normal baseline enzymes or *greater than* 10-fold elevations from their baseline values of AST and/or ALT in patients w/ elevated transaminase enzymes at baseline

The baseline mean AST and ALT values in the three cohorts are summarized in the following table.

Table 13. Mean Baseline Hepatic Transaminase Levels in Study Conducted by Chalasani et al.⁶

	Cohort 1 n=342	Cohort 2 n=1437	Cohort 3 n=2245
AST (IU/L)	55±37	22 ± 7	57 ± 49
ALT (IU/L)	43 ± 23	20 ± 8	61 ± 47

* the upper limits of normal for AST and ALT were 40 and 35 IU/L, respectively

The frequency of mild to moderate and severe transaminase elevations in the 3 cohorts is summarized in the following table:

Table 14.

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.

Patients with baseline elevated hepatic transaminase elevations had significantly higher rate of mild to moderate elevations with statin therapy compared to patients who had normal baseline values treated with statins. (Cohort 1 vs. Cohort 2). However, there were no differences in enzyme elevations between Cohort 1 and patients who had baseline enzyme elevations who were not treated with statins (Cohort 3). The authors stated that this finding might suggest that mild-to-moderate elevations in transaminase elevations may be independent of statin exposure and reflect more the natural course of the medical condition resulting in baseline transaminase elevations. While this may be a logical conclusion, patients with certain known liver conditions were excluded from this study.

These authors also compared Cohort 1 to an additional control group consisting of 1,111 individuals with detectable hepatitis C antibody (not treated with statins or interferon) who had elevated baseline AST or ALT. Compared with Cohort 1, individuals with hepatitis C had a significantly higher frequency of mild-to-moderate or severe elevations in liver biochemistries. This comparison provided no safety data for *statin use in patients with chronic hepatitis C*.

The applicant reviewed the worldwide adverse experience safety database for selected hepatobiliary adverse experience. As of June 1, 2003, there were 25 cases of hepatic failure/hepatic necrosis and 251 reports of "hepatitis" reported for lovastatin. Given an estimated worldwide exposure to lovastatin of approximately 27 million patient-years, the calculated reporting rate of hepatic failure/hepatic necrosis and "hepatitis" is 1.0 and 10.4 reports, respectively, per million patient-years of treatment.

Similarly, the FDA's Office of Drug Safety searched AERS for domestic reports of liver failure associated with statin use. Three preferred terms were used in the search criteria: liver failure, hepatic encephalopathy, and liver transplant. A consult was conducted in March 2001 and updated recently in November 2004. As of February 25, 2000, there were 14 domestic reports of liver failure associated with lovastatin use. As of November 5, 2004, there were 20 reports. Reporting rates were calculated for the 4-year period post-approval in the March 2001 consult. As summarized by the FDA epidemiologist, the reporting rate for lovastatin was estimated at 2 cases per million person-years of exposure which approximates the background rate of idiopathic liver failure of approximately 1 per 1,000,000 person-years.

In conclusion, transaminase elevations occur with statin therapy; however, large databases from clinical trials and postmarketing use suggest that these increases rarely result in serious liver injury and in the few reports of liver injury, attribution to statin use cannot be established. While such data would strongly support the recommendation that post-baseline monitoring be obtained only when clinically indicated, the Agency has conveyed to the applicant that information is needed to determine if baseline monitoring is still required to identify those patients with asymptomatic liver disease. These chronic liver diseases would include nonalcoholic fatty liver disease (NAFLD), hepatitis C, hepatitis B, and alcoholic liver disease in which the patient may be unaware of their condition. It has been estimated that NAFLD affects 10 to 24% of the general population and that 1.8% of the U.S. population is positive for hepatitis C antibodies.^{7,8} In a

⁷ Angulo, P. Nonalcoholic fatty liver disease. *NEJM*. 346(16): 1221-1231.

supplement submitted to the prescription NDA for lovastatin, the applicant is proposing the WARNINGS section of the label include the following modification:

This supplement is still under review; however, it should be noted that the proposed language will not remove baseline monitoring for lovastatin. The proposed label recommends that the prescriber consider a patient's history of/for liver disease and obtain the laboratory tests prior to initiating drug therapy. In the nonprescription setting, this recommendation would also require the applicant to demonstrate that consumers can identify whether they have a history of liver disease, risk factors for liver disease, or clinical signs and symptoms suggestive of liver disease to decide if they should obtain baseline LFTs prior to purchasing and using the product.

VI. COMMENTS ON NONPRESCRIPTION MEVACOR 20 MG PROGRAM

The October 2000 non-approval letter to the applicant stated that “*neither the rationale for treating the proposed target population with Mevacor 10 mg in the over-the-counter (OTC) setting, nor a favorable benefit/risk ratio for such treatment has been adequately established. Furthermore, the ability of consumers to appropriately self-select and to adequately comply with chronic Mevacor therapy without the intervention of a physician has not been demonstrated*”.

In this resubmission to NDA 21-213, the applicant has selected a patient population that has “*≥ 2 risk factors for CHD and a ≤ 20% risk of CHD over 10 years without underlying chronic conditions that complicate consumer self-management*”. Based on NCEP ATP-III guidelines, these are individuals in which lipid-altering drug therapy should be considered if, after therapeutic lifestyle changes, LDL-C remains ≥ 130 (or ≥ 160 if 10-year risk for CVD is $< 10\%$). The treatment goal for these individuals is an LDL-C goal of < 130 mg/dL. The applicant has proposed that a daily fixed dose of lovastatin 20 mg will effectively treat this population with respect to meeting LDL-C goals and CHD risk reductions.

Data from controlled clinical trials, in particular, AFCAPS/TexCAPS, suggest that lovastatin 20 mg daily will allow a majority of OTC-eligible patients to achieve an LDL-C goal of < 130 mg/dL. Based on a post-hoc analysis of a subgroup of AFCAPS/TexCAPS patients and a non-randomized comparison, the sponsor proposes that among approximately 28 individuals achieving such an LDL-lowering effect and complying with the daily treatment regimen for up to 6 years, data from AFCAPS suggest that one atherosclerotic event will be prevented. The extent of population benefit and of individual risk reduction with lesser degrees of compliance and shorter terms of treatment is not known.

Data from controlled clinical trials and post-marketing spontaneous adverse event reporting support the conclusion that risks of muscle and hepatic toxicity are rare events that do not offset the benefits associated with long-term use of lovastatin 20 mg in

⁸ Lauer, GM and Walker BD. Hepatitis C virus infection. *NEJM*. 345(1):41-52.

otherwise healthy individuals. The hepatic risks of lovastatin 20 mg daily in patients with baseline liver disease of certain etiologies have been addressed in the amended application, though no prospective investigations in patients with diverse forms of asymptomatic liver disease have been conducted. The extent to which the data presented can be extrapolated to the types of liver disease generally prevalent in the OTC target population must be considered. Other safety concerns include drug-drug interactions which affect the risk of myopathy and exposure during pregnancy. The sponsor proposes to manage these risks through labeling.

The Rx-to-OTC switch of Mevacor 20 mg must not engender novel or augmented risks nor significantly undermine effectiveness of the drug in the prevention of cardiovascular disease. For optimally safe use, the consumer must appropriately self-select as eligible for therapy after excluding factors that would increase the risk of drug side effects (e.g., pregnancy, liver disease) and elect discontinuation of therapy when situations arise that would alter the risk of therapy (e.g., newly prescribed interacting drug, development of myopathy). For optimal efficacy and avoidance of undertreatment, the consumer must appropriately self-select based on LDL level and CVD risk factor profile, must seek follow up and take appropriate action based on response (e.g., discontinue and seek physician intervention if response is inadequate). Additionally, the consumer should understand that management of hypercholesterolemia is chronic. Adherence to medications and compliance to diet and life-style modifications are essential components of this management. Consumers must also understand that their individual risks for heart disease may change over time based on age, development of heart disease, or other factors (e.g., elevated blood pressure, development of diabetes). With these changes, consumers must understand that target therapies may be lower and that they may have to seek appropriate management to achieve these new goals. Finally, the field of lipid biology, atherosclerosis, and CV risk management will evolve over time as new data emerge. A nonprescription program that will be affected by changing treatment guidelines must be adaptable to these and other changes in the state of the relevant basic and clinical science in order to ensure appropriate consumer behavior and ongoing safety and efficacy of the OTC treatment regimen.