

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 19766, S34

Trade Name: ZOCOR TABLETS

Generic Name: SIMVASTATIN

Sponsor: MERCK & CO, INC.

Approval Date: 11/22/99

**INDICATION(s): TREATMENT OF PATIENTS WITH
ISOLATED HYPERTRIGLYCERIDEMIA
(FREDRICKSON TYPE IV) (S-34)***

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 19766, S34

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter				X
Printed Labeling				X
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative/ Correspondence Document(s)	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 19766, S-34

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-766/S-034, S-036

Merck & Co., Inc.
Attention: Robert Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4
BLA-20
West Point, PA 19486

NOV 22 1999

Dear Dr. Silverman:

Please refer to your supplemental new drug applications dated January 21, 1999, received January 22, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

We acknowledge receipt of your submissions dated January 21(second submission) and November 16, 1999.

These supplemental new drug applications provide for a new indication for the treatment of patients with isolated hypertriglyceridemia (Fredrickson Type IV) (S-034) and for a new indication for the treatment of Type III hyperlipoproteinemia (S-036).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted November 16, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-766/S-034, S-036." Approval of these submissions by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the

requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until March 31, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

NDA 19-766/S-034, S-036
Page 3

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Management Officer,
at (301) 827-6418.

Sincerely,

/s/

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19766, S-34

MEDICAL REVIEW(S)

NDA 19-766/S-034

Zocor (simvastatin) tablets

Merck

Category: Lipid altering/HMG-CoA reductase inhibitor

Indication: treatment of patients with isolated hypertriglyceridemia (Fredrickson Type IV)

Date of submission: January 21, 1999

Date of review: November 12, 1999

Medical Team Leader review

Introduction

Isolated hypertriglyceridemia due to elevations in VLDL, IDL, and remnant lipoproteins (Type IV) and accompanied by low HDL-C and small, dense LDL particles is associated with increased risk for atherosclerosis. Marked hypertriglyceridemia (total TG > 1500-2000 mg/dL) is further associated with a risk of pancreatitis. Elevation in triglycerides to these levels is, virtually by definition, indicative of the presence of chylomicrons (Type V). Patients will often see-saw between these two phenotypes with chylomicronemia precipitated commonly by dietary indiscretion and alcohol use.

In the past, the epidemiologic association between elevated TG levels and risk for CHD has been a point of argument, as it holds most consistently only in univariate analyses. This is because of the close correlation between elevated TG levels and low HDL-C, itself a strong predictor of heart disease risk. Furthermore, elevated plasma TG are often found in association with non-lipid metabolic risk factors for coronary heart disease. In addition, prospective studies specifically examining the impact on CHD risk of TG lowering in patients with Type IV are lacking. This is not to say there are no suggestive interventional data. In the Helsinki Heart Study, for example, the overall trial outcome was driven by the results in patients with the triad of moderately elevated LDL-C, elevated TG, and low HDL-C. Despite this and other suggestive evidence, until recently (the label for Lipitor tablets was amended in 1998), labeling regarding efficacy in TG lowering in patients with Type IV has avoided the issue of impact on CHD risk. More specifically, drugs with demonstrated effectiveness in lowering TG levels (e.g., niacin, fibrates) have been labeled for patients with hypertriglyceridemia at risk for pancreatitis.

It is important to point out that despite the implication of such labeling, studies assessing effects of these agents on pancreatitis risk have neither been required by the Division nor are otherwise forthcoming from clinical investigators. In fact, most of the patients in pivotal proof-of-efficacy trials for TG-lowering drugs have had TG levels below 1500 mg/dL (which does not pose a major risk of pancreatitis). Indeed, by the very nature of the patient population with elevated TG, both niacin and fibrates are most frequently used and are most effective in patients with Type IV HLP not obviously at risk for pancreatitis. In fact, drug therapy is usually ineffective in patients with Type V hyperlipoproteinemia and marked elevations in TG due to chylomicronemia. Thus, irrespective of labeling, the rationale for the major use of these drugs in patients with isolated hypertriglyceridemia is

the presumption that lowering levels of TG-rich lipoproteins in many patients with Type IV HLP is of benefit in that it likely reduces CHD risk.

The current supplement proposes a new indication for the use of simvastatin in patients with Type IV HLP. The assessment of the appropriateness of such labeling depends on the strength of the lipid altering data and not on any evidence of reduction in the risk of pancreatitis. Again, the true rationale for treating such patients is to reduce heart disease risk. The database in support of this indication is quite small. All told, it includes 74 patients with isolated hypertriglyceridemia treated with simvastatin in a three-period randomized, placebo-controlled, crossover design. The acceptability of this relatively small exposure in support of a new indication is based on several factors. First of all, the safety profile of simvastatin across the dosage range has been established on the basis of a very large (many thousands of patients) controlled clinical trial experience. Second, there appears to be no difference in the tolerability of the drug in patients with hypercholesterolemia, mixed dyslipidemia, or isolated hypertriglyceridemia. Finally, the efficacy with regard to lipid altering is clearly demonstrated in this small cohort of patients, with an understanding that summary statistics of central tendency may not fully describe the expected response to therapy. Because of small numbers of patients as well as variability in response to drug in patients with elevated TG, the data may well need to be described in more detail in labeling.

Review of the lipid altering data in the patients with Type IV, particularly with regard to the changes in non-HDL-C, an indicator of atherogenic particle burden in patients with mixed dyslipidemia, suggest that simvastatin is a useful adjunct to diet in these patients, not to reduce the risk of pancreatitis, but to lower the atherogenicity of plasma. As such, the indication for use of this and other statins should dispense with the reference to pancreatitis risk. To the extent that definitive interventional trials have not been conducted, however, a statement to the effect that the independent effect of TG lowering on CV morbidity and mortality has not been determined should be included in labeling and should accompany any promotion of this and other drugs for the treatment of these patients (already included in labeling).

Methods

Study design

Study 133 was randomized 3-period, placebo-controlled, crossover study of 130 patients with combined hyperlipidemia. There was a 4-week diet/placebo run-in period followed by three 6-week treatment periods of placebo, simvastatin 40 mg daily, or 80 mg daily in six unique sequences. The primary endpoint of the study was change from baseline in LDL-C. A subset of 74 patients with Type IV HLP (LDL-C <160 mg/dL with TG > 200 mg/dL) was identified and their lipid data analyzed for the current supplement.

Disposition

Of the 74 patients with Type IV, 68 completed all 3 treatment periods.

Results

Of the 74 patients, 43 (58%) were male. 67 (91%) were Caucasian. Sixty-four (86%) were aged between 41 and 70. Baseline mean levels of TG, TC, LDL-C, HDL-C, and non-HDL-C were, respectively, 426, 265, 134, 38, and 227 mg/dL. The range of baseline TG levels among the 74 patients was 243-1089 mg/dL.

The following table, reproduced from the submission, summarizes the lipid-response data in the Type IV patients.

	Baseline (mg/dL)	Mean percent change from baseline to week 6 N=67-72 per group		
		Simva 40	Simva 80	Placebo
TG*	404	-29	-34	-8.9
TC	265	-26	-31	1.0
LDL-C	134	-28	-35	2.9
VLDL-C*	83	-37	-41	-6.5
Non-HDL-C	228	-32	-39	0.4
Apo B	152	-22	-29	3.9
HDL-C	38	13	14	4.1
Apo A-1	140	7.9	10	4.5

*median or median percent change

All values for active-treated groups were statistically significantly different from placebo. For TC, LDL-C, non-HDL-C, and apo B, the differences between simva 40 and 80 mg groups were also statistically significant.

The following table summarizes the median (min, max) percent changes from baseline for the principal lipids and lipoproteins measured in the study.

Safety

The spectrum and frequency of adverse events in this study was consistent with the labeling for simvastatin. One patient on simvastatin 80 mg daily had persistent elevations of both ALT and AST to > 3X ULN that resolved on discontinuation of therapy. There were no clinically important elevations in CK or cases of myopathy. There is no evidence from this submission that simvastatin is either better or worse tolerated in patients with hypertriglyceridemia than in any other group of dyslipidemic patients.

Discussion and Conclusions

In patients with hypertriglyceridemia (Type IV), dysbetalipoproteinemia (Type III), and mixed dyslipidemia (Type IIb), lowering of total TG, VLDL-C, IDL-C is a target as well as presumptive evidence of benefit of treatment. However, because of the tendency of some drugs, notably fibrates and niacin, to increase LDL-C levels in patients with elevated levels of TG-rich lipoproteins, it is often more telling to examine the effect of therapy on

non-HDL-C, derived simply by subtracting the HDL-C level from the total-C level. Changes in non-HDL-C will roughly parallel those for TG, VLDL-C, and IDL-C as increases in LDL-C are usually only modest in absolute magnitude. Indeed, in patients with Type IV, even marked percentage increases in LDL-C are small, in absolute terms, because of low baseline LDL-C levels.

The results for changes in non-HDL-C in the patients with Type IV show that although variable, all patients showed a reduction with simvastatin treatment. Because only two doses of simvastatin were studied, a dose-response cannot be concluded from these data. Based on the known mechanism of lipid altering of statins, namely the combined effects of increased LDL-receptor-mediated clearance of apo B-containing lipoproteins and decreased synthesis and secretion of VLDL from the liver, it is not unreasonable to expect that, as for TC and LDL-C, so, too, would there be a reliable dose response to simvastatin for non-HDL-C in these patients. This is mentioned merely to make the point that simvastatin should be titrated to optimum effect in these patients as in those with Types IIa and IIb HLP. Thus no specific instructions in Dosage and Administration need be written for the Type IV patients. These data are further supportive of a role for simvastatin in the primary therapy of some patients with isolated hypertriglyceridemia. A trial of simvastatin therapy in these patients is justified on the basis of the current data.

Labeling

Clinical Pharmacology, first paragraph

The involvement of LDL-C in atherogenesis has been well documented in clinical and pathological studies, as well as in many animal experiments. Epidemiologic studies have established that high LDL-C, low HDL-C, and high plasma triglycerides are risk factors for CHD. Cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma triglycerides (TG) are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Clinical Pharmacology, Clinical Studies, Coronary Heart Disease

First paragraph

See review of S-037

Hypertriglyceridemia (Fredrickson Type IV)

Text acceptable. Table 2 should contain the median (min, max) % change from baseline rather than the mean % change from baseline.

Dysbetalipoproteinemia (Fredrickson Type III)

Labeling and table acceptable. See review for S-036.

Indications and Usage

Labeling acceptable

Precautions, Drug Interactions, Other concomitant therapy
See review for S-038.

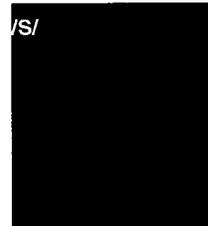
Recommendation

Pending agreement on labeling, this supplement may be approved.

David G. Orloff, M.D.
Medical Team Leader
DMEDP/CDER/FDA

Recommendation code: AP

cc:
NDA 19-766 Arch
HFD-510
HFD-510: Simoneau/Parks



APPEARS THIS WAY ON ORIGINAL

November 21, 1999

Memorandum

To: the File NDA 19,766 Supplements 034 and 036

From: Solomon Sobel M.D. Director, Division of Metabolic and
Endocrine Drug Products

Subject: Approval of supplements

These supplemental new drug applications provide for a new indication for the treatment of patients with isolated hypertriglyceridemia (Fredrickson Type IV) (S034) and for a new indication for the treatment of Type III hyperlipoproteinemia (S-036)

The Sponsor agreed to our suggested labeling changes and presentations in the clinical pharmacology section on November 18, 1999.

The difficulties encountered with the small data bases especially in respect to the very rare Type III hyperlipidemia were well addressed.

Conclusion:

The Division has concluded that both Supplements may be approved.

/S/

Solomon Sobel M.D.

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19766, S-34

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION CDER/HFD-510 Division of Metabolism and Endocrine Drug Products		2. NDA # 19-766 Original NDA approved: 23-DEC-1991	
3. NAME AND ADDRESS OF APPLICANT Merck & Co., Inc. P.O. Box 4 West Point PA 19486 (Phone): 610-397-2944		4. SUPPLEMENT SEI-034, -036	
		5. Name of the Drug ZOCOR™	
		6. Nonproprietary Name Simvastatin	
7. SUPPLEMENT PROVIDES an Efficacy Supplement for addition of the indication of treatment of Fredrickson Types IV and III hyperlipidemia		8. AMENDMENT --	
9. PHARMACOLOGICAL CATEGORY HMG-CoA inhibitor used to treat hyperlipidemia	10. HOW DISPENSED Oral	11. RELATED -N. A. -	
12. DOSAGE FORM Tablet	13. POTENCY 5, 10, 20, 40 & 80 mg		
14. CHEMICAL NAME AND STRUCTURE Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8α-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*,4S*),-8αβ]]; C ₂₅ H ₃₈ O ₅ , F.W. = 418.57, CAS 56180-94-0 (For the structure, see Chemistry Review #1, dated 16-MAR-1988 in Vol. 3.1 of NDA 19-766).			
15. COMMENTS			
16. CONCLUSIONS AND RECOMMENDATIONS The request for a Categorical Exclusion to prepare an EA under 21 CFR §25.31(b) is acceptable. From a Chemistry point of view, these supplements can be approved. Issue approval letter.			
17. REVIEWER NAME (AND SIGNATURE) COMPLETED 20-OCT-1999 Sharon Kelly, PhD /s/ [Redacted] R/D INITIATED BY [Redacted]		DATE <i>Oct 20, 1999</i>	
filename: 19766NDASup			
DISTRIBUTION: Original: sNDA 19-766 cc: HFD-510 Division File CSO Reviewer			

AP [Redacted]
/s/ [Redacted]
10/20/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19766, S-34

PHARMACOLOGY REVIEW(S)

NDA 19-766/S-034

Review Completed: April 9, 1999

Sponsor: Merck & Co., Inc.; P.O. Box 4; West Point, PA 19486

PHARMACOLOGY REVIEW OF NDA SUPPLEMENT
Supplement to NDA 19-766 S #034 (January 21, 1999)

DRUG: Zocor™, Simvastatin

CATEGORY: HMG CoA Reductase Inhibitor, "statin"

Supplement #034 for NDA 19-766 (Zocor™, (simvastatin)) provides for addition of the indication of treatment of Fredrickson Types IV and III hyperlipidemia to the *HYPERLIPIDEMIA* subsection of the INDICATIONS AND USAGE section of the label. Additional changes to the clinical sections of the label were made. There were no pharmacology/toxicology studies submitted to this supplement and none were required. There were no changes made to the preclinical sections of the label. There is no need for further action from pharmacology.

/s/

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

4/9/99

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19766, S-34

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

November 17, 1999

NOV 22 1999

APPROVED

Merck & Co., Inc. *ORLOFF*
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

Solomon Sobel, MD, Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-041
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20850



Dear Dr. Sobel:

NDA 19-766/S-034: ZOCOR™
NDA 19-766/S-036: ZOCOR™
(Simvastatin)

Labeling Sept 99
ISI
11-18-99

Amendment to Supplemental Application

Reference is made to the above Supplemental New Drug Applications (SNDAs) originally submitted by Merck Research Laboratories (MRL), a Division of Merck & Co. Inc., on January 21, 1999, proposing new indications for the treatment of Fredrickson Type III and IV hyperlipidemia; a series of telephone conversations between Dr. Silverman (MRL) and Dr. Orloff between November 1 and November 12 regarding the proposed product labeling; and a telefax from Dr. Silverman to Ms. Simoneau (FDA) on November 16, 1999 containing modified draft product labeling reflecting the negotiations between Drs. Silverman and Orloff.

By this letter and attachment, MRL is amending the above noted SNDAs with a new proposal for product labeling (clean running text attached) that conforms to the draft provided by MRL on November 16, 1999.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

A handwritten signature in black ink, appearing to read 'Robert E. Silverman', written over a horizontal line.

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

Attachment

Desk Copy: Dr. David Orloff, HFD-510, Rm 14B-04 (with attachments)
Ms. Margaret Simoneau, HFD-510, Rm. 14B-04 (with attachments)

Federal Express #1
q/shilling/ta/683

ZOCOR®
NDA 19-766
Simvastatin

Item 13

December 15, 1998

ITEM 13
PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

- | | | |
|----|--|---|
| 1) | Active Ingredient(s) | Simvastatin |
| 2) | Strength(s) | 5 mg, 10 mg, 20 mg, 40 mg and 80 mg |
| 3) | Trade Name | ZOCOR® |
| 4) | Dosage Form, Route
of Administration | Tablets, Oral |
| 5) | Applicant Firm Name | Merck Research Laboratories |
| 6) | NDA Number | 19-766 |
| 7) | Approval Date | |
| 8) | Exclusivity - Date First
ANDA could be approved | Three (3) Years from this SNDA
approval date |
| 9) | Applicable patent numbers
and expiration date of each | 4,444,784
Expiration Date: 12/23/2005 w/PTR |

Patent Department

Merck & Co., Inc.
P.O. Box 2000
Rahway NJ 07065-0907
Fax 732 594 4720
Tel 732 594 4000
Cable MERCKRAH
Telex 138825



December 15, 1998

ZOCOR®
NDA 19-766
Simvastatin

Item 14

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act 21 U.S.C. § 355 (b)(1) and in accordance with Title 21 C.F.R. 314.70(b), attached hereto please find the patent information for the above-identified application.

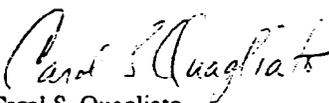
The undersigned declares that U.S. Patent No. 4,444,784 covers the formulation, composition, and/or method of use of ZOCOR® (simvastatin 5 mg, 10 mg, 20 mg, 40 mg and 80 mg tablets), the subject of this application for which approval is being sought.

U.S. Patent No. 4,444,784, has an expiration date of Decemoer 23, 2005, as extended by granted Patent Term Restoration under 35 U.S.C. § 156. This patent claims a genus of chemical compounds including simvastatin. This patent is exclusively licensed to Merck & Co., Inc.

The undersigned declares that U.S. Patent No. 4,444,784 covers the composition ZOCOR®. This product is the subject of this application for which approval is being sought.

A claim of infringement could be asserted if a person not licensed by the owner of U.S. Patent No. 4,444,784 engaged in the manufacture, use or sale of ZOCOR®.

Sincerely,


Carol S. Quagliato
Senior Patent Attorney

EXCLUSIVITY SUMMARY FOR NDA # 19-766

SUPPL # 034
Fredrickson Type IV

Trade Name Zocor

Generic Name Simvastatin Tablets

Applicant Name Mack

HFD # 510

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES // NO //

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

no

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES // NO //

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES // NO //

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

NA

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

APPEARS THIS WAY ON ORIGINAL

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

2. Combination product. *N/A*

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO //

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO //

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

133-01 Subgroup II Type II

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

not this specific subgroup

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

133-01 subgroup / Type II

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
 IND # [redacted] YES / / ! NO / ___ / Explain: _____
 !
 !

Investigation #2 !
 IND # _____ YES / ___ / ! NO / ___ / Explain: _____
 !
 !

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
 YES / ___ / Explain _____ ! NO / ___ / Explain _____
 !
 !
 !

Investigation #2 !
 YES / ___ / Explain _____ ! NO / ___ / Explain _____
 !
 !
 !

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO /

If yes, explain: _____

/s/ [Redacted]

Signature
Title: _____

11/16/99

Date

/s/ [Redacted]

Signature of Office/
Division Director

11/21/99

Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

APPEARS THIS WAY ON ORIGINAL

Simvastatin Type IV/Type III Hyperlipidemia
Item 16 - Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

APPEARS THIS WAY ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-766/S-036 [REDACTED]

JUN 8 1999

Merck Research Laboratories
Attention: Charles Hyman, M.D.
Sumneytown Pike P.O. Box 4
Westpoint, PA 19486

Dear Dr. Hyman:

We acknowledge receipt of your supplemental applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zocor (simvastatin) Tablets

NDA Number: 19-766

Supplement Numbers: S-034, S-036 [REDACTED]

Date of Supplements: January 21, 1999

Date of Receipt: January 22, 1999

Our review of the changes proposed in your submission indicates that they must be administratively unbundled into four supplements

These supplements propose the following changes:

Supplement-034 adds the new indication, treatment of patients with Fredrickson Type IV hypertriglyceridemia.

Supplement-036 adds the new indication, treatment of patients with Fredrickson Type III hyperlipidemia.

Supplement-037 proposes to incorporate in the CLINICAL PHARMACOLOGY section data from the Scandinavian Simvastatin Survival Study (4S) on the prevention of coronary heart disease (CHD) in patients with type 2 diabetes mellitus

Supplement-038 proposes to create a new subsection, "Other Concomitant Therapy" for the PRECAUTIONS section, to contain a list of commonly-prescribed concomitant medications.

NDA 9-766/S-036

Page 2

Clinical data are required to support S-034, S-036. A user fee is assessed for each supplement that requires the review of clinical data. The appropriate user fee was paid for Supplement-034.

review. Thus, payment of a user fee for Supplement-036 is now due. Please obtain a new user fee identification number for Supplement-036 and submit a User Fee Cover Sheet for that supplement.

Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by courier should be delivered to:

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number is on the enclosed check.

These applications were filed under section 505(b) of the Act on June 1, 1999, in accordance with 21 CFR 314.101(a). The primary user fee goal date will be February 2, 2000, and the secondary user fee goal date will be April 2, 2000.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response

whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely yours,

/s/ [REDACTED]

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 9-766/S-036 [REDACTED]

Page 4

APPEARS THIS WAY ON ORIGINAL

cc:

Archival NDA 19-766/ S-034,-036 [REDACTED]

HFD-510/Div. Files

HFD-510/M. Simoneau

HFD-510/Reviewers and Team Leaders

HFD-5/User Fee staff

DISTRICT OFFICE

Drafted by: emg/May 25, 1999

final: emg/6.8.99

filename: 19766S34

ACKNOWLEDGMENT (AC)

APPEARS THIS WAY ON ORIGINAL

Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2310
215 652 5000
Email larry_bell@merck.com

January 21, 1999

These copies are OFFICIAL FDA Copies
not desk copies.

Solomon Sobel, M.D. - Director
Division of Metabolism and Endocrine
Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, Maryland 20850

NDA SUPP AMEND

581-034 ZM



NDA 19-766: ZOCOR™
(Simvastatin)

Supplemental New Drug Application

By copy of this letter, Merck Research Laboratories (MRL), a division of Merck & Co. Inc., is providing to the Technology Support Service Staff (TSSS) one (1) Compact Disk (CD) which contains a supplemental New Drug Application (sNDA) for NDA 19-766: ZOCOR™ (Simvastatin), submitted in hardcopy on January 21, 1999.

This supplemental application supports the addition of the treatment of patients with Fredrickson Types IV and III hyperlipidemia to the *Hyperlipidemia* subsection of the INDICATIONS AND USAGE section of the ZOCOR™ label. Changes are also proposed to the CLINICAL PHARMACOLOGY section on the prevention of coronary heart disease (CHD) in patients with type 2 diabetes mellitus and to the PRECAUTION section to add a list of commonly-prescribed concomitant medications with simvastatin under a new subsection, *Other Concomitant Therapy*.

The information on the CD (Serial No. NL8B-P035-2474) is to be copied to the StorageWorks Building Block (SBB) (Serial Number NI708Z5513) currently installed on the MRL-dedicated network server in use at the Agency for the Simvastatin Type IV/Type III Hyperlipidemia sNDA.

A list of reviewers from the Metabolic & Endocrine Drug Products Division who should be provided access to this electronic submission from their desktops may be obtained from Ms. Margaret Simoneau, Project Manager.

Please notify MRL's Regulatory Agency Relations (RAR) Office (301/881-9000) when the disk installations are successfully completed and access from the reviewers' desktops is functional.

When an action has been taken on this submission and the CD is no longer needed, MRL will make arrangements to retrieve the CD from the FDA. We understand that, in the future, information submitted in electronic form may be retained indefinitely by the Agency, as an archival copy of the application, in the event that a complete paper submission is not filed.

We have taken precautions to ensure that any software on the CD is free of computer viruses and we authorize the use of anti-virus software, as appropriate.

Solomon Sobel, M.D. - Director
NDA 19-766: ZOCOR™
Page 2

There are five attachments to this letter:

- Attachment 1 An NDA Table of Contents of the accompanying electronic submission.
- Attachment 2 A Difference Report identifying differences between the electronic version of this submission and the hard copy submission.
- Attachment 3 Installation Instructions detailing how to copy the contents of the CD onto the server.
- Attachment 4 Documentation regarding the development procedures performed at MRL for this electronic submission.
- Attachment 5 A complete list of file names.

During the time that the electronic submission is actively being used, MRL will provide technical support. Any questions relating to this electronic submission should be addressed to me (610/397-2310) or, in my absence, Margo Herron (301/881-9000).

Sincerely,



Larry Bell, M.D.
Senior Director
Regulatory Affairs

Q:\murakami\zocor\III,IV\admin\ElecCov

Attachments
Enclosures: Compact Disk
Serial No. NL8B-P035-2474

Federal Express #1

cc (cover letter only):

K. Edmunds, Division of Technology Support Services Staff, HFD-70 Federal Express #2

S. Sobel, M.D. - HFD-510, Room 14B-04; Federal Express #3

M. Simoneau - HFD-510, Room 14B-04, Federal Express #3

cc (cover letter with attachments):

NDA 19-766, HFD-510 (2 copies), Federal Express #4

DUPLICATE

Charles L. Hyman, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2850
215 652 5000

NDA NO. 19-766 REF NO. 034
NDA SUPPL FOR §81



January 21, 1999

Solomon Sobel, M.D. - Director
Division of Metabolism and Endocrinology
Drug Products HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

**Supplemental New Drug Application
NDA 19-766: Tablets ZOCOR™ (simvastatin)
User Fee No. 3643**

Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and in accordance with 21 CFR 314.70 (b), Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. is submitting a Supplemental New Drug Application (sNDA) for ZOCOR™ (simvastatin).

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in Labeling and Clinical Documentation of the approved New Drug Application (NDA) for Tablets ZOCOR™.

Reference is made to the letter dated July 10, 1998 in which FDA references NDA 19-766 and requests MRL submit a supplemental application to support an indication for the treatment of patients with isolated hypertriglyceridemia (Fredrickson Type IV) at risk for coronary heart disease (CHD).

In response to the FDA's request, the supplemental application included herein provides data to support the addition of treatment of patients with Fredrickson type IV and also type III hyperlipidemia to the *Hyperlipidemia* sub-section of the INDICATIONS AND USAGE section of the ZOCOR™ label. In addition, this application also proposes to incorporate data from the Scandinavian Simvastatin Survival Study (4S) on the prevention of CHD in patients with type 2 diabetes mellitus to the CLINICAL PHARMACOLOGY section, and also provide a list of commonly-prescribed concomitant medications with simvastatin in a new sub-section of the PRECAUTION section, *Other Concomitant Therapy*.

CLIN=REF

SE1
SE1

SEE →
SLR

Solomon Sobel, M.D. - Director
Supplemental New Drug Application
NDA 19-766: Tablets ZOCOR™ (Simvastatin)
User Fee No. [REDACTED]
Page 2

In type IV hyperlipidemia, elevated levels of triglyceride-rich lipoproteins and associated small, dense low-density lipoprotein cholesterol (LDL-C) particles and low high-density lipoprotein cholesterol (HDL-C) levels contribute to the enhanced risk of CHD. In type III hyperlipidemia, there is direct evidence that accumulated remnant lipoproteins are atherogenic. For both populations, data demonstrating the salutary effects of simvastatin on the lipoprotein profiles of these patients are derived from a subset of patients who participated in a randomized, double-blind, placebo-controlled dose ranging study of patients with combined hyperlipidemia. The results of this study (Protocol No. 133) have previously been submitted to the agency in support of extending the *Hyperlipidemia* indication to incorporate the raising of HDL (SNDA 19-766/S-032, submitted October 16, 1998). Subgroup data from this study (Protocol No. 133) concerning 74 patients meeting the lipid criteria for type IV hyperlipidemia (i.e., TG above 200 mg/dL and LDL-C below 160 mg/dL) and 8 with type III hyperlipidemia are provided to support these new indications.

Diabetes mellitus is a potent risk factor for CHD. A post-hoc sub-group analysis of 202 diabetic patients in the Scandinavian Simvastatin Survival Study (4S) found that treatment with simvastatin reduced their risk of CHD by more than half (55%). We believe the substantial benefit to this subgroup should be noted along with other sub-group results from 4S that are included in the *Clinical Studies* sub-section of the CLINICAL PHARMACOLOGY section of the label.

The last proposed change is to develop a new sub-section, *Other Concomitant Therapy* in the PRECAUTION section. This sub-section proposes to list drugs commonly used with simvastatin in the Scandinavian Simvastatin Survival Study (4S). Currently, the product circular provides explicit information on drugs such as potent inhibitors of CYP 3A4, which should not be taken concomitantly with simvastatin because of the concern for increasing the risk of myopathy and rhabdomyolysis. However, no information is provided in the label about drugs which are commonly prescribed to patients who would also require treatment with simvastatin. Some of these drugs such as the calcium channel blockers verapamil, diltiazem and nifedipine may also be weak CYP 3A4 inhibitors. The information we propose adding to the label reflects controlled clinical trial experience from 4S with commonly used concomitant medications including calcium channel blockers. We believe such information could prove useful to prescribing physicians.

This application is formatted as required in Title 21, paragraph 314.50 of the Code of Federal Regulations. It consists of a complete "archival" copy (Blue Binders), comprising five (5) volumes and one "review" copy (Light brown Binders) of the Clinical Documentation section consisting of four (4) volumes and a copy of Volume 1 containing Item 1 and Item 2 as described in the Statement of Organization which is attached to this letter. In addition, this sNDA is being provided simultaneously in both paper copy and electronic format.

Solomon Sobel, M.D. - Director
Supplemental New Drug Application
NDA 19-766: Tablets ZOCOR™ (Simvastatin)
User Fee No. [REDACTED]
Page 3

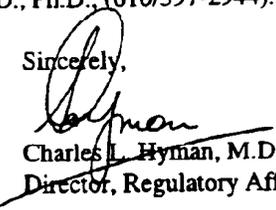
In accordance with the Food and Drug Administration Modernization and Accountability Act of 1997 (FDAMA), a check for this Supplemental New Drug Application in the amount of [REDACTED] (Check No. [REDACTED] User Fee I.D. No. [REDACTED] was sent to the Mellon Bank, Three Mellon Bank Center, 27th Floor (FDA 360909), Pittsburgh, PA 15259-0001, on January 13, 1999.

Merck & Co., Inc. is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(b). The production of ZOCOR™ (simvastatin) meets the requirements of a categorical exclusion under 21 CFR §25.31(b) because the estimated concentration of drug substance, simvastatin, at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment will be below [REDACTED]. In arriving at the EIC, metabolism of simvastatin to less pharmacologically active or inactive compounds was considered. To the best of the firm's knowledge no extraordinary circumstances exist in regards to this action.

We consider the filing of this New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its existence public without first obtaining written permission from Merck & Co., Inc.

Questions concerning this information should be directed to Charles L. Hyman, M.D. (610/397-2850) or, in my absence, Robert E. Silverman, M.D., Ph.D., (610/397-2944).

Sincerely,


Charles L. Hyman, M.D.
Director, Regulatory Affairs

Attachment
Federal Express #1
Desk Copy (Letter and Patent Information Only):
Ms. Mary Ann Holovac, HFD-93
5600 Fishers Lane,
Rockville, MD 20857
Federal Express #2

Desk Copy (Letter Only):
Dr. David Orloff, HFD-510, Rm. 14B-04
Federal Express #1
Ms. Margaret Simoneau, HFD-510, Rm. 14B-04
Federal Express #1