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)*
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 19766, S-34

APPROVAL LETTER
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

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

Sincerely,

[Signature]

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

<table>
<thead>
<tr>
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<th>Baseline (mg/dL)</th>
<th>Simva 40</th>
<th>Simva 80</th>
<th>Placebo</th>
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<td>TG*</td>
<td>404</td>
<td>-29</td>
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<td>TC</td>
<td>265</td>
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<td>VLDL-C*</td>
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<tr>
<td>Non-HDL-C</td>
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<td>-32</td>
<td>-39</td>
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<tr>
<td>Apo B</td>
<td>152</td>
<td>-22</td>
<td>-29</td>
<td>3.9</td>
</tr>
<tr>
<td>HDL-C</td>
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<td>13</td>
<td>14</td>
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<tr>
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<td>140</td>
<td>7.9</td>
<td>10</td>
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</table>

*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 hypertriglyceridermia than in any other group of dyslipidemic patients.

Discussion and Conclusions
In patients with hypertriglyceridermia (Type IV), dysbetalipoproteinemia (Type III), and mixed dyslipidemia (Type IIIb), 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

NDA 19-766/S-034
Zocor in Type IV
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.

Dysbeta lipoproteinemia (Fredrickson Type III)
Labeling and table acceptable. See review for S-036.

Indications and Usage
Labeling acceptable

NDA 19-766/S-034
Zocor in Type IV
Precautions, Drug Interactions, Other concomitant therapy
See review for S-038.

Recommendation
Pending agreement on labeling, this supplement may be approved

Recommendation code: AP

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

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

11-12-99

APPEARS THIS WAY ON ORIGINAL

NDA 19-766/S-034
Zocor in Type IV
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.

/\ 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**

<table>
<thead>
<tr>
<th>1. ORGANIZATION</th>
<th>CDER/HFD-510 Division of Metabolism and Endocrine Drug Products</th>
</tr>
</thead>
</table>
| 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*)] C25H38O5, 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) | Sharon Kelly, PhD |
| REVIEWED BY | |
| R/D INITIATED BY | |
| COMPLETED | 20-OCT-1999 |
| DATE | Oct 29, 1999 |

filename: 19766NDASup

**DISTRIBUTION:** Original: sNDA 19-766  
c: HFD-510 Division File  
CSO Reviewer

AP  
\[\text{Date: } 10/1/2019\]
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19766, S-34

PHARMACOLOGY REVIEW(S)
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.

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader
4/9/99
APPLICATION NUMBER: 19766, S-34
November 17, 1999

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)

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,

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
qisullivan/10/663
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    Expiration Date: 12/23/2005 w/PTR
December 15, 1998

ZOCOR®
NDA 19-766
Simsatatin

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 December 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
Trade Name Zocor
Generic Name Simvastatin Tablets
Applicant Name Merck
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

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac
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. 

   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 / ___/

Page 5
(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

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 /__/  

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"):  

[Handwritten text] 133-01  

Page 7
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 |        | NO /__/ Explain: __________ |
| IND # [redacted] | YES /✓ / |                          |
| Investigation #2 |        | NO /__/ Explain: __________ |
| IND # [redacted] | YES /__/ |                          |

(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 |        | NO /__/ Explain: __________ |
| YES /__/ Explain: ______ |                          |
| Investigation #2 |        | NO /__/ Explain: __________ |
| YES /__/ 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: ________________________________

[Signature] [Signature of Office/Division Director]

Title: ________________________________ Date: 11/14/99

Date: 11/21/99

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

APPEARS THIS WAY ON ORIGINAL
PEDiatric PAGe

(COnplete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

[ Handwritten: 19-766 9-36 ]

Trade and generic names/dosage form: Recombinant Human Factor VIII

Applicant: [Handwritten: McKee; Lupin, Loven, R. Ds]

Therapeutic Class: Factor VIII (Human), FVIII (human), FVIII:Ag, FVIII:Antihemophilic Factor

Indication(s) previously approved: [Handwritten: Hemophilia A]

Pediatric information in labeling of approved indication(s) is adequate: [Handwritten: Inadequate]

Proposed indication in this application: [Handwritten: Type III Hyperlipoproteinemia (S-036)]

Type III Hyperlipoproteinemia (S-036)

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUP? [Handwritten: Yes] (Continue with questions) [Handwritten: No] (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

- Neonates (Birth-1 month)
- Infants (1 month-2 yrs)
- Children (2-12 yrs)
- Adolescents (12-16 yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

   - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
   - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
   - c. The applicant has committed to doing such studies as will be required.
      - (1) Studies are ongoing.
      - (2) Protocols were submitted and approved.
      - (3) Protocols were submitted and are under review.
      - (4) No protocol has been submitted, attach memo describing status of discussions.
   - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? [Handwritten: Yes] [Handwritten: No]

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from: [Handwritten: Med. Team Lead (e.g., medical review, medical officer, team leader)]

[Handwritten: 11/16/97]

Signature of Preparer and Title [Handwritten: [Blank]]

Orig NDA/BLA #: [Handwritten: [Blank]]

HF: [Handwritten: Div File]

NDA/BLA Action Package

HFD-0801 KRuthefs

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD 6 (ROBERTS)
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.
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

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 hypertriglyceridermia.

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.
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
2/F 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 website 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,

/signed/

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

CC:
Archival NDA 19-766/ S-034.,-036
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: 19766534

ACKNOWLEDGMENT (AC)

APPEARS THIS WAY ON ORIGINAL
January 21, 1999

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 19-766: ZOCORT™ (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: ZOCORT™ (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 ZOCORT™ 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. NL88-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.
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

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
January 21, 1999

Solomon Sobel, M.D. - Director
Division of Metabolism and Endocrine
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 ZOCORT™ (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 ZOCORT™ (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 ZOCORT™.

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 ZOCORT™ 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.
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—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 lists 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 be 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.
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

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 ZOCORTM (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 

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