

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number: 19766, S36**

**Trade Name: ZOCOR TABLETS**

**Generic Name: SIMVASTATIN**

**Sponsor: MERCK & CO, INC.**

**Approval Date: 11/22/99**

**INDICATION(s): A NEW INDICATION FOR THE  
TREATMENT OF TYPE III HYPERLIPOPROTEINEMIA  
(S-36)**

# CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 19766, S36

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Printed Labeling				X
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number: 19766, S-36**

**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](http://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-36**

**MEDICAL REVIEW(S)**

**NDA 19-766/S-036 (SE1)**  
**Zocor (simvastatin) tablets**  
**Merck & Co., Inc.**  
**Category: Lipid altering**  
**Proposed new indication: treatment of Type III hyperlipoproteinemia**  
**Date of submission: January 21, 1999**  
**Date of review: November 12, 1999**

**Background**

Type III hyperlipoproteinemia (familial dysbetalipoproteinemia) occurs at a rate of approximately 1 in 10,000 people and is diagnosed on the basis of elevated total cholesterol and triglycerides in the setting of an abnormal apolipoprotein E phenotype by isoelectric focusing. Specifically, affected individuals carry abnormal allele(s) for apo E and are either homozygous (90%) or heterozygous for apo E2, which, because of its reduced affinity for the LDL receptor, results in impaired clearance of chylomicron and VLDL remnants. In the context of associated metabolic abnormalities, as obesity, Type 2 DM, hypothyroidism, of excessive alcohol intake, or other monogenic or polygenic dyslipidemias, all sharing the common characteristic of increased hepatic VLDL production and/or impaired lipoprotein-lipase-mediated VLDL catabolism, individuals with these apo E genotypes develop increased plasma levels of remnant lipoproteins, evident as increased cholesterol, TG, VLDL, IDL, and by a "broad-beta" pattern on lipoprotein electrophoresis.

Remnant hyperlipoproteinemia is associated with accelerated atherosclerosis involving the coronary and peripheral arteries, often more prominent in the latter, and is thus an indication for diet modification with or without lipid altering drug therapy. Current treatment in addition to diet includes fibrates, nicotinic acid, fish oil, and HMGRI. While clinical endpoint trials have not been conducted in the relatively small population of patients with Type III HLP, all evidence suggests that lowering levels of cholesterol and TG in these patients, indicative of a decrease in IDL and thus in the burden of circulating atherogenic particles, would lead to a reduction in risk for atherosclerosis-related clinical events.

The currently accepted primary therapies for Type III hyperlipoproteinemia, the fibric acid derivatives, acting through PPAR $\alpha$ , increase the expression of lipoprotein lipase (LPL), decrease transcription of the apoC-III gene, and induce transcription of apoA-I and A-II genes. The results of these molecular effects are principally to induce lipolysis of TG on TG-rich lipoprotein remnants (the consequence of increased LPL as well as better accessibility of TG-rich, apoC-III depleted lipoproteins to lipolysis), and to reduce hepatic TG synthesis and thus VLDL production. In the context of adequate synthesis of apoA-I and A-II, lower levels of TG-rich remnants also result in increases in HDL-C. Newer fibrates have an additional effect to lower LDL-C by increased clearance via the LDL receptor. This is felt due to fibrate associated changes in LDL composition and structure that enhance the affinity of LDL for its receptor. Finally, the literature supports changes in the LDL particle phenotype with fibrate therapy from atherogenic, small-dense to less

atherogenic, large-buoyant, because lipolysis of VLDL-TG is restored toward normal with these agents.

**Background data (published)**

In a study of 19 patients with homozygosity for apo E2, simvastatin 20 mg daily for 8 weeks effected changes in total-C, VLDL-C, LDL-C, HDL-C and TG of -41%, -48%, -43%, +26%, and -39%, respectively. Simvastatin 40 mg resulted in additional favorable changes in all lipid parameters. Addition of gemfibrozil 450 mg daily to simvastatin 40 mg daily resulted in modest further reductions in TC, VLDL, and TG, but also reduction HDL-C and increased LDL-C in some patients (see references).

In a second crossover study, 12 Type III patients were treated sequentially with 20, 40, and 80 mg of simvastatin. At the 80 mg dose, mean changes from baseline in TC, TG, HDL-C, LDL-C and VLDL-C were, respectively, -54%, -48%, +8%, -41%, -70% (see references).

**Clinical data submitted with this application**

The sponsor has submitted lipid-response and safety data from 7 patients with Type III HLP, culled from a larger trial of simvastatin (Protocol 133, A multicenter, randomized, double-blind, placebo-controlled, 3-period, balanced, crossover study to evaluate the efficacy of simvastatin therapy in patients with combined hyperlipidemia). Eight patients with Type III were retrospectively identified based on elevated TC and TG, apo E2/2 genotype, and a VLDL-C/TG ratio > 0.25. One of the patients withdrew from the study during the first treatment period and thus is not included in the final analysis.

**Protocol 133: Combined hyperlipidemia study**

**Design**

After a 4-week diet/placebo run-in, eligible patients were randomized to 1 of 6 treatment sequences, each consisting of three 6-week treatment periods of placebo, S40, and S80 in 6 different orders. There were no washout periods between treatment periods.

**Inclusion criteria**

Men and women 21-70 years of age with CHL defined as LDL-C >130 mg/dL, TG between 300 and 700 mg/dL at weeks -4 and -2.

**Results for the 7 Type III patients**

The table below is reproduced from the submission.

Table 1. Changes in plasma lipid in patients with Type III HLP from study 133

	Baseline median Mg/dL	Median % change (min, max) from baseline		
		Simvastatin 40 N=7	Simvastatin 80 N=7	Placebo N=7
Total-C	324	-50 (-66, -39)	-52 (-55, -41)	-7.6 (-24, +34)
LDL-C	121	-50 (-60, -31)	-51 (-57, -28)	-8.1 (-27, +23)
VLDL-C	170	-58 (-90, -37)	-60 (-72, -39)	-3.8 (-28, +78)
Non-HDL-C	291	-57 (-72, -44)	-59 (-61, -46)	-8.3 (-26, +39)
HDL-C	31	6.7 (-7.7, +23)	6.7 (-4.8, +29)	-1.6 (-21, +16)
TG	411	-41 (-74, -16)	-38 (-58, 2.3)	+3.5 (-22, +90)
Apo B	116	-40 (-56, -28)	-44 (-51, -34)	-2.6 (-22, 17)
Apo E	72	-38 (-75, -26)	-50 (-64, -16)	+9.5 (-5.5, +71)

No direct measurements of IDL were performed for this study. Since most of the non-HDL-associated cholesterol is carried in VLDL and IDL in these patients, the changes in non-HDL-C are a valid reflection of the changes in levels of VLDL-C and to a great extent, IDL-C. Type III patients do not have elevated levels of LDL-C, the mean baseline LDL-C in this small cohort being 125 mg/dL. Levels of apo B and E are elevated in these patients and reflect the burden of atherogenic remnant lipoproteins. The marked reductions in levels of these apoproteins is therefore a reflection of the reduction in remnant lipoprotein particles.

For TC, LDL-C, VLDL-C, TG, non-HDL-C, apo E, and apo B, the changes from baseline in the simvastatin groups were statistically significantly different from placebo.

This application contains no clinical outcome data, nor any investigations comparing simvastatin to other accepted treatments for Type III, as fibric acid derivatives or niacin, with regard to lipid altering efficacy.

#### Safety

Simvastatin was well tolerated in this small cohort of patients. There were no episodes of myopathy or CK elevations > 10X ULN and no patients who experienced consecutive AST or ALT elevations >3 X ULN.

#### Labeling review

Clinical Pharmacology, first paragraph

Editorial revisions are acceptable except for last sentence of paragraph.

The independent effect of .... has not been definitively determined in prospective clinical studies.

Clinical Studies, Coronary Heart Disease, first paragraph, last sentence.

(See review for S-037)

Clinical studies, Primary hypercholesterolemia.

Editorial revisions are acceptable.

**Clinical studies, Hypertriglyceridemia (Fredrickson Type IV)**

Table 2 should show median (min, max) % changes from baseline for TG, TC, LDL-C, HDL-C, VLDL-C, and non-HDL-C.  
(See review for S-034)

**Clinical studies, Dysbetalipoproteinemia (Fredrickson Type III)**

Text and Table 3 are acceptable.

**Precaution, Drug interactions, Other concomitant therapy**

See review for S-038.

**Recommendations**

With respect to labeling that relates to the studies of patients with Type III HLP, because of the small number of patients, the great variability in response to treatment, median percent and ranges of percent changes should be cited instead of mean percent changes from baseline. The disclaimer in approved labeling regarding the absence of data on the cardiovascular morbidity and mortality benefits of Zocor treatment should follow the statement of the effect of Zocor in patients with dysbetalipoproteinemia.

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 Arch 19-766  
HFD-510  
HFD-510: Hennan/Simoneau

IS/

1212-99

11.21.99

**References:**

Feussner G, et al. Clinical features of type III hyperlipoproteinemia: analysis of 64 patients. Clin Investig 1993, 71: 362-366.

Feussner G, et al. The influence of simvastatin alone or in combination with gemfibrozil on plasma lipids and lipoproteins in patients with type III hyperlipoproteinemia. Clin Investig 1992, 70: 1027-1035.

Stuyt PM, et al. Simvastatin in the effective reduction of plasma lipoprotein levels in familial dysbetalipoproteinemia (Type III hyperlipoproteinemia). Am J Med 1990; 88: 42n-45n.

Fruchart JC et al. Consensus for the use of fibrates in the treatment of dyslipoproteinemia and coronary heart disease. Am J Cardiol 1998, 81: 912-917.

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-36**

**CHEMISTRY REVIEW(S)**

**CHEMIST'S REVIEW**

<b>1. ORGANIZATION</b> CDER/HFD-510 Division of Metabolism and Endocrine Drug Products		<b>2. NDA #</b> 19-766 Original NDA approved: 23-DEC-1991	
<b>3. NAME AND ADDRESS OF APPLICANT</b> Merck & Co., Inc. P.O. Box 4 West Point PA 19486 (Phone): 610-397-2944		<b>4. SUPPLEMENT</b> SEI-034, -036	
		<b>5. Name of the Drug</b> ZOCOR™	
		<b>6. Nonproprietary Name</b> Simvastatin	
<b>7. SUPPLEMENT PROVIDES</b> an Efficacy Supplement for addition of the indication of treatment of Fredrickson Types IV and III hyperlipidemia		<b>8. AMENDMENT</b> --	
<b>9. PHARMACOLOGICAL CATEGORY</b> HMG-CoA inhibitor used to treat hyperlipidemia	<b>10. HOW DISPENSED</b> Ofal	<b>11. RELATED</b> -N. A. -	
<b>12. DOSAGE FORM</b> Tablet	<b>13. POTENCY</b> 5, 10, 20, 40 & 80 mg		
<b>14. CHEMICAL NAME AND STRUCTURE</b> Butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8 $\alpha$ -hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl-ester, [1S-[1 $\alpha$ ,3 $\alpha$ ,7 $\beta$ ,8 $\beta$ (2S*,4S*),-8 $\alpha$ $\beta$ ]]; C <sub>25</sub> H <sub>38</sub> O <sub>5</sub> , 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).			
<b>15. COMMENTS</b>			
<b>16. CONCLUSIONS AND RECOMMENDATIONS</b> 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.			
<b>17. REVIEWER NAME (AND SIGNATURE)</b> COMPLETED 20-OCT-1999 Sharon Kelly, PhD R/D INITIATED BY		<b>DATE</b>  OCT 20, 1999	
filename: 19766NDASup			
DISTRIBUTION: Original: sNDA 19-766 cc: HFD-510 Division File CSO Reviewer			

AP  
/SI  
1 10/20/99

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 19766, S-36**

**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*  
[Redacted] *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'.

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/tz/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<br>of Administration                  | Tablets, Oral                                   |
| 5) | Applicant Firm Name                                      | Merck Research Laboratories                     |
| 6) | NDA Number   | 19-766  |
| 7) | Approval Date  |   |
| 8) | Exclusivity - Date First<br>ANDA could be approved       | Three (3) Years from this SNDA<br>approval date |
| 9) | Applicable patent numbers<br>and expiration date of each | 4,444,784<br>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.

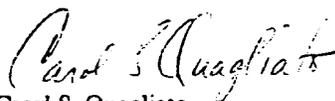
The undersigned declares that U.S. Patent No. 4,444,784 covers the formulation, composition, and/or method of use of ZOCOR® (simvastatin 5 mg, 10 mg, 20 mg, 40 mg and 80 mg tablets), the subject of this application for which approval is being sought.

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 e 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 // *Not this specific subgroup.*

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"):

133-01 subgroup of Type III

\_\_\_\_\_

\_\_\_\_\_

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: \_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Signature  
Title: \_\_\_\_\_

11/16/99  
\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Office/  
Division Director

11/21/99  
\_\_\_\_\_  
Date

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

APPEARS THIS WAY ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 19-766

SUPPL # 036

Type III hyperlipoproteins

Trade Name Zcor

Generic Name Simvastatin Tablets

Applicant Name MEACK

HFD # S10

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.

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 /  /

NA

APPEARS THIS WAY ON ORIGINAL

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

NDA# \_\_\_\_\_ N/A  
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:

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(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:

Subgroup 2 Study 133-01  
\_\_\_\_\_

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 //

*not for this  
particular  
subgroup*

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"):

133-01

\_\_\_\_\_

\_\_\_\_\_

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 \_\_\_\_\_  
 !  
 !  
 !  
 !



PEDIATRIC PAGE

(Complete 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.

NDA/BLA # 19-766

Supplement 036 Circle one (SE1) SE2 SE3 SE4 SE5 SE6

Trade and generic names/dosage form: ZECOR (Simvastatin) AP AE NA

Applicant MERCK Therapeutic Class Lipid Lowering Drugs

Indication(s) previously approved Patents w/ CHD + ACS Fredrickson Type IIa+b; homozygous familial hypercholesterolemia

Pediatric information in labeling of approved indication(s) is adequate inadequate

Proposed indication in this application FREDRICKSON TYPE 4 (S-034)

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 GROUPS? Yes (Continue with questions) No (Sign and return the form)

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

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

- 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.
2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.
3. PEDIATRIC STUDIES ARE NEEDED.
4. 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? Yes No

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

This page was completed based on information from Med. Team Ldt (e.g., medical review, medical officer, team leader)

Signature of Preparer and Title Date 11/16-99

Orig NDA/BLA #
HF /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

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.

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  
27<sup>th</sup> 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](http://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  
SE2

SES  
SLR

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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.

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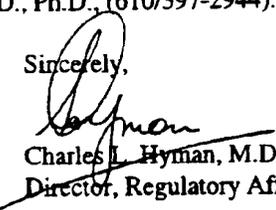
In accordance with the Food and Drug Administration Modernization and Accountability Act of 1997 (FDAMA), a check for this Supplemental New Drug Application in the amount of [REDACTED] (Check No. [REDACTED] User Fee I.D. No. [REDACTED]) was sent to the Mellon Bank, Three Mellon Bank Center, 27th Floor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