

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019766/ S026/S028

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

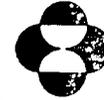
Charles L. Hyman, M.D.
Director
Regulatory Affairs

DESK COPY

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

July 2, 1998

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



MERCK
Research Laboratories

APPEARS THIS WAY
ON ORIGINAL

*Label OK.
7/2/98*

Dear Dr. Sobel:

**NDA 19-766/S-026: ZOCOR® (Simvastatin)
General Correspondence**

Reference is made to the above Supplemental New Drug Application (SNDA). Reference is also made to an annotated label that was submitted for review on June 25, 1998, and a telephone conversation between Dr. David Orloff, Food and Drug Administration (FDA), and Dr. Charles Hyman, Merck Research Laboratories (MRL), on June 25, 1998, during which Dr. Orloff accepted this label as submitted with the exception of the proposed second sentence on Page 7. Additional changes to the annotated label submitted on June 25, 1998 were discussed. Reference is further made to a fax sent by the Agency to MRL on June 26, 1998 which confirmed the acceptance of the label submitted on June 25, with the proviso that the proposed alternative second sentence on Page 7 be removed, and that the subsection titled **Other Concomitant Therapy** under the **Precautions/Drug Interactions** section will be deleted as per previous agreement.

APPEARS THIS WAY
ON ORIGINAL

By this letter, MRL is submitting for your review a label for ZOCOR in annotated and clean running format that incorporates all the previously agreed upon labeling revisions for this supplement including those additional changes discussed with Dr. Orloff on June 25, 1998, and reiterated in the fax of June 26, 1998. Please note we are providing these changes in the current circular (7825429) as opposed to the circular in use at the time of this supplement's submission (7825423) on August 4, 1997.

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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..

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S. Sobel, MD, Director
NDA 19-766/S-026: ZOCOR
July 2, 1998
Page Two

If you have further questions or need additional information, please contact Charles L. Hyman, M.D. (610) 397-2850 or, in my absence, Bonnie J. Goldmann, M.D., (610) 397-2383.

Sincerely,



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

APPEARS THIS WAY
ON ORIGINAL

Hand Delivered by Ms. Marie Dray

Desk Copies (hand delivered):

Dr. David Orloff, HFD-510, Rm. 14B-04

Ms. Margaret Simoneau, HFD-510, Rm. 14B-04

clh/fah
hark\zoc\fd\041L.doc

APPEARS THIS WAY
ON ORIGINAL

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

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
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These copies are OFFICIAL FDA Copies
not desk copies.

June 25, 1998



Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

APPEARS THIS WAY
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Dear Dr. Sobel:

**NDA 19-766/S-026: ZOCOR® (Simvastatin)
General Correspondence**

Reference is made to the above Supplemental New Drug Application (SNDA). Reference is also made to an annotated label, dated June 23, 1998, and submitted for review on June 24, 1998, and a telephone conversation between Dr. David Orloff, Food and Drug Administration (FDA), and Dr. Charles Hyman, Merck Research Laboratories (MRL), on June 24, 1998, during which additional changes to the annotated label submitted were discussed. By this letter, MRL is resubmitting for your review an updated annotated label for ZOCOR that incorporates those additional changes discussed with Dr. Orloff on June 24, 1998.

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 further questions or need additional information, please contact Charles L. Hyman, M.D. (610) 397-2850 or, in my absence, Robert E. Silverman, M.D., Ph.D. (610) 397-2944.

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

Margo E. Herron
for Charles L. Hyman, M.D.
Charles L. Hyman, M.D.
Director
Regulatory Affairs

Hand Delivered by Ms. Margo Herron

Desk Copies (hand delivered):

Dr. David Orloff, HFD-510, Rm. 14B-04
Ms. Margaret Simoneau, HFD-510, Rm. 14B-04

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clh/fah
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ZOCOR®
NDA 19-766
Simvastatin

Item 13

April 2, 1997

ITEM 13
PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

- | | | |
|----|---|---|
| 1) | Active Ingredient(s) | Simvastatin |
| 2) | Strength(s) | 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 or Five (5) Years from 12/23/91 (12/23/96) |
| 9) | Applicable patent numbers and expiration date of each | 4,444,784 Expiration Date: 12/23/2005 w/PTR |

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ON ORIGINAL

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ON ORIGINAL



April 2, 1997

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ON ORIGINAL

Item 13

ZOCOR®
NDA 19-766
Simvastatin

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 80 mg tablet), 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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 19-766 SUPPL # 026 #028

Trade Name Zocor Generic Name SIMVASTATIN
Applicant Name MERCK HFD-510

Approval Date _____

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 questions about the submission.

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

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

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

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.

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:

d) Did the applicant request exclusivity?

YES / / NO / /

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

3 per 21 CFR 314.108 (b)(4)

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?

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).

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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 / /

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

NDA # 19-766 Zocor

NDA # _____

NDA # _____

APPEARS THIS WAY
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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 # _____

APPEARS THIS WAY
ON ORIGINAL

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 / /

APPEARS THIS WAY
ON ORIGINAL

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 / /

APPEARS THIS WAY
ON ORIGINAL

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:

APPEARS THIS WAY
ON ORIGINAL

- _____
- _____
- (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:

Investigation #1, Study # 114

Investigation #2, Study # _____

Investigation #3, Study # _____

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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 / <input checked="" type="checkbox"/> / | NO / <input type="checkbox"/> / |
| Investigation #2 | YES / <input type="checkbox"/> / | NO / <input type="checkbox"/> / |
| Investigation #3 | YES / <input type="checkbox"/> / | NO / <input type="checkbox"/> / |

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

NDA # 14-766 Study # 114
 NDA # _____ Study # _____
 NDA # _____ Study # _____

APPEARS THIS WAY
ON ORIGINAL

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 / <input type="checkbox"/> / | NO / <input checked="" type="checkbox"/> / |
| Investigation #2 | YES / <input type="checkbox"/> / | NO / <input type="checkbox"/> / |
| Investigation #3 | YES / <input type="checkbox"/> / | NO / <input type="checkbox"/> / |

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

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

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ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

- 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"):

Investigation # 1, Study # 114

Investigation # , Study #

Investigation # , Study #

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ON ORIGINAL

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 # 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?

N/A

Investigation #1

YES / / Explain ! NO / / Explain

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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.

DA/BLA # 14-766

Supplement # 26 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF S10 Trade and generic names/dosage form: ZOCOR (SIMVASTATIN) Action: AP AE NA

Applicant MERCK Therapeutic Class Lipid Lowering Drugs

Indication(s) previously approved _____

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

Proposed indication in this application FOR THE TREATMENT OF PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA AND A NEW HIGHER STRENGTH OF SIMVASTATIN TABLETS, 80mg

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. 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) If 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/biologic 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? ___ Yes No

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

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

-/S/
Signature of Preparer and Title

6-29-98
Date

Orig NDA/BLA # 14-766

HF S10 /Div File

NDA/BLA Action Package

HFD-006/ KRoberts

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

(revised 10/20/97)

NDA SUPPLEMENT

ORIGINAL

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

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

NDA NO. 19766 REF. NO. 026

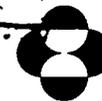
NDA SUPPL FOR 422

August 4, 1997

NDA NO. 19766 REF. NO. 028

NDA SUPPL FOR 305

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



MERCK

Research Laboratories

Dear Dr. Sobel:

**Supplemental New Drug Application
NDA 19-766: Tablets ZOCOR™ (Simvastatin)**



Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Merck Research Laboratories (MRL) 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 Item(s) 3, 4, 6, 8, 10, 11, 12, and 13 of the approved New Drug Application for Tablets ZOCOR™.

NDA 19-766 for Tablets ZOCOR™, 5, 10, 20 and 40 mg was approved on December 23, 1991. ZOCOR™, also referred to as simvastatin, MK-0733 and L-644,128 is an inhibitor of hydroxymethylglutaryl coenzyme A (HMG-CoA) and is currently used to treat hypercholesterolemia and reduce cardiovascular mortality and morbidity in patients with cardiovascular disease.

This application supports the use of simvastatin tablets, 80 mg and proposes changes to various section of the product label to reflect this new information. Development of simvastatin tablets, 80 mg has evolved from the earlier development of lower strength tablets of simvastatin that are approved for marketing. Extending the dosage range of simvastatin will allow even more effective reduction of elevated LDL-cholesterol in appropriate patients.

Studies used to assess the cholesterol-lowering efficacy of simvastatin 80 mg/day include two Phase III studies (Protocol 117-06 U.S. and 117-07 Non-U.S.), the Phase IIb and extension studies (Protocols 111 and 111-10), and the male adrenal gonadal study (Protocol 123).

On November 3, 1995, Merck Research Laboratories held an End-of-Phase II meeting with FDA during which the proposed clinical programs designed to support the expansion of the dosage range for simvastatin to 80 mg daily were presented. A letter to the FDA dated December 15, 1995, documented an agreement which was reached between the Agency and MRL in reference to a waiver of the requirement for data from the 12 month market container stability studies since the 80 mg formulation is an exact weight multiple of the currently marketed 40 mg formulation. MRL will provide six month market container stability data with the initial submission of the simvastatin - 80 mg SNDA and will submit the market container stability up to 12 months during the Agency review period.

On May 29, 1996 in a telephone conversation held between Drs. Robert E. Silverman (MRL) and William Berlin (Reviewing Chemist-FDA), the Agency agreed to accept a biobatch quantity of 75,000 for the 80 mg formulation of ZOCOR™. In a follow-up telephone conversation on June 18, 1997, Dr. Berlin agreed that production of commercial product could be conducted at a larger batch size (450,000) provided that product equivalency for the two batch sizes (75,000 tablets and 450,000 tablets) be demonstrated.

On January 17, 1997, a letter was submitted to Ms. Deborah Browning, Division of Emergency and Investigational Operations, documenting the concurrence between the Agency and MRL that, at time of filing the simvastatin - 80 mg SNDA, the pre-approval inspection and a validation protocol will be available, but that the validation of the process will not be completed.

Simvastatin drug substance used in the manufacture of simvastatin tablets, 80 mg will be manufactured by Merck & Co., Inc., One Merck Drive, P.O. Box 100, Whitehouse Station, NJ 08889-0100, utilizing the facilities located at one or more of

Manufacturing of simvastatin tablets, 80 mg will be conducted at Merck Sharp & Dohme (MSD) Shotton Lane, Cramlington, Northumberland NE23 9JU, United Kingdom. Release testing may be performed at either MSD

Packaging of simvastatin tablets, 80 mg will be conducted at Merck & Co., 4633 Merck Road, Wilson, NC 27893.

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 32 volumes and four "review" copies as described in the Statement of Organization which is attached to this letter.

This NDA is being provided in electronic format and hard copy with the exception of Items 11 and 12 (case report tabulation and forms). Items 11 and 12 are being provided in electronic format only, for which a formal waiver from the requirements of 21 CFR 314.50(f) has been approved (FDA approval letter dated May 29, 1997) in accordance with current CDER policy.

The electronic format of this submission will be submitted on or about August 18, 1997 to the FDA Division of Information Systems Design (DISD). MRL will contact the FDA to arrange an orientation to the electronic submission for all relevant Agency reviewers. Any differences between the hard copy and the electronic version will be noted in the documentation accompanying the electronic version. Copies of the documentation provided with the electronic submission will also be submitted to the NDA.

In accordance with the Prescription Drug User Fee Act of 1992, a check for this SNDA in the amount of _____ was sent to the Mellon Bank, Three Mellon Bank Center, 27th Floor (FDA 360909), Pittsburgh, PA 15259-0001, on July 21, 1997.

Pursuant to 21 CFR 314.50(k)(3), a complete field copy of the Chemistry, Manufacturing and Controls technical section (Item 3) has been submitted to the FDA Philadelphia District Office (Attention: Ms. Debra L. Pagano). This field copy is a true copy of Item 3 as contained in the archival copy and review copies of this application.

Merck affirms that all sites listed in this application to support the manufacturing, packaging and labeling of ZOCOR™ for the market are available for pre-approval inspection at the time of this submission.

As required by Section 306(k)(1) of the Generic Enforcement Act [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.

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 Robert E. 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

APPEARS THIS WAY
ON ORIGINAL

/ltr/mcs/467
Attachment
Hand Delivered

Desk Copy: (Item 3)
Philadelphia District Office, Attn.: Ms. Debra L. Pagano
U.S. Custom House Room 900, 2nd & Chestnut Streets
Philadelphia, PA 19106-2973
Federal Express #1

Desk Copy (Letter and Patent Information Only):
Mr. George Scott, HFD-984, 5516 Nicholson Lane, Rm. 238,
Rockville, MD 20857
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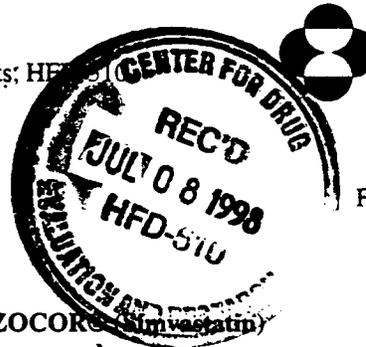
Charles L. Hyman, M.D.
Director
Regulatory Affairs

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

July 7, 1998

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products; HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



MERCK
Research Laboratories

Fax: 301.443.9282

Dear Dr. Sobel:

NDA 19-766/S-026: ZOCORE (simvastatin)
General Correspondence

Reference is made to the above Supplemental New Drug Application (SNDA). Reference is also made to a facsimile recommendation sent by the Agency to MRL on July 2, 1998, and the MRL response to this recommendation dated July 6, 1998, in which MRL acknowledged the need to investigate the current

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 further questions or need additional information, please contact Charles L. Hyman, M.D. (610) 397-2850 or, in my absence, Bonnie J. Goldmann, M.D., (610) 397-2383.

Sincerely,

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

Federal Express #1

Desk Copies:

Federal Express #1 Dr. David Orloff, HFD-510, Rm. 14B-04
Federal Express #1, Ms. Margaret Simoneau, HFD-510, Rm. 14B-04
Federal Express #2, Dr. Hae Young Ahn, HFD-870, Rm. 14B-18

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

DESK COPY

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

July 6, 1998

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Fax: 301.443.9282

Dear Dr. Sobel:

**NDA 19-766/S-026: ZOCOR® (Simvastatin)
General Correspondence**

**APPEARS THIS WAY
ON ORIGINAL**

Reference is made to the above Supplemental New Drug Application (SNDA). Reference is also made to facsimile sent by the Food and Drug Administration (Agency) to Merck Research Laboratories (MRL) on July 2, 1998.

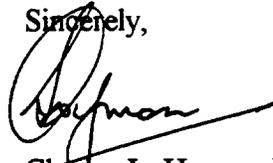
We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc..

**APPEARS THIS WAY
ON ORIGINAL**

S. Sobel, MD, Director
NDA 19-766/S-026: ZOCOR
July 6, 1998
Page Two

If you have further questions or need additional information, please contact Charles L. Hyman, M.D. (610) 397-2850 or, in my absence, Bonnie J. Goldmann, M.D., (610) 397-2383.

Sincerely,



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

APPEARS THIS WAY
ON ORIGINAL

Federal Express #1

Desk Copies:

Federal Express #1, Ms. Margaret Simoneau, HFD-510, Rm. 14B-04
Federal Express #1 Dr. David Orloff, HFD-510, Rm. 14B-04

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APPEARS THIS WAY
ON ORIGINAL

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

June 26, 1998

DESK COPY

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Via Fax: 301.443.9282

Dear Dr. Sobel:

APPEARS THIS WAY
ON ORIGINAL

**SNDA 19-766/S-026: ZOCOR® (simvastatin)
Response to Question**

Reference is made to the above Supplemental New Drug Application (SNDA). Reference is also made to a letter submitted by Merck Research Laboratories (MRL) on June 10, 1998, in which MRL provided an explanation for the apparent discrepancy in pharmacokinetic profiles (AUC and Cmax) of ZOCOR 80 mg between Protocols #111 and #120 included in this submission, and those from original NDA studies. Reference is further made to telephone conversations between Dr. Robert Shore of the Food and Drug Administration (FDA), and Dr. Charles Hyman of MRL on June 24 and June 25, 1998, during which this apparent discrepancy in pharmacokinetic profiles was further discussed and Dr. Shore requested additional data regarding the pharmacokinetic profiles (AUC and Cmax) of ZOCOR. By this letter, MRL is providing the requested additional data.

The attachments provide the following data:

Attachment 1:

Summary of all control data from pharmacokinetic interaction studies with ZOCOR performed subsequent to the original NDA.

Attachment 2A & 2B:

Summary of AUC of total inhibitors and Cmax of total inhibitors from all studies generating such data that were included in the original NDA.

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..

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ON ORIGINAL

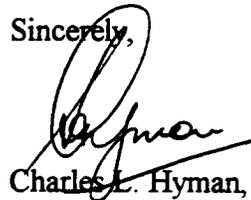
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Letter to: S. Sobel, MD, Director
NDA 19-766/S-026: ZOCOR® 80 mg
June 26, 1998
Page Two

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..

We believe this explanation satisfies your request. If you have further questions or need additional information, please contact 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

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ON ORIGINAL

Attachments

Certified Mail #: P 967 678 169

Desk Copy:

Certified Mail #: P 967 678 170 Ms. Margaret Simoneau, HFD-510, Rm. 14B-04

Certified Mail #: P 967 678 171 Dr. Robert Shore, HFD-870, Rm. 14B-04

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ATTACHMENT I

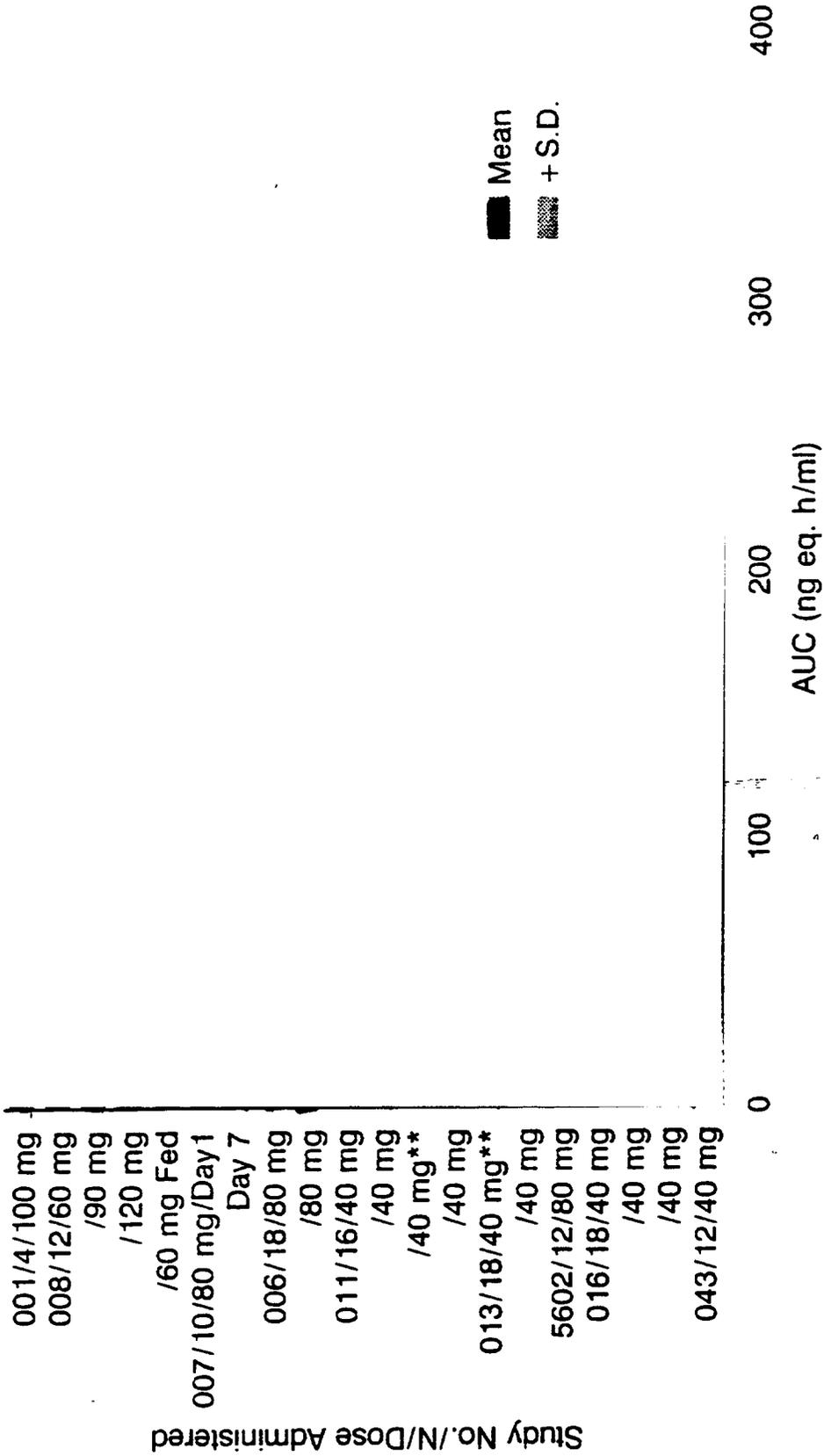
Summary of AUC and C_{max} Data for Recent Studies Using ZOCOR Doses of 40 or 80 mg

| Study # | Year | Formulation | P/S | Dose, mg | AUC tot | C _{max} tot | AUC active | C _{max} active |
|------------------------|-----------|-------------|-----|----------|---------|----------------------|------------|-------------------------|
| 031* N=9M & 9F | 1990-1991 | Tablets | | 40 | | | | |
| | | | | 40 | | | | |
| 072 MODS | 1991 | Tablets | | 20(40) | | | | |
| | | | | | | | | |
| 121* | 1996-1997 | Tablets | | 80(40) | | | | |
| 127 FormComp | 1996-1997 | Tablets | | 80(40) | | | | |
| 131 FormComp | 1997 | Tablets | | 80(40) | | | | |
| 139 Itra | 1997-1998 | Tablets | | 80(40) | | | | |
| 148 Mibef | 1998 | Tablets | | 20(40) | | | | |
| 141 Troglit | 1997-1998 | Tablets | | 40 | | | | |
| 138* Atorva Comp | 1998 | Tablets | | 80(40) | | | | |
| | | | | 80(40) | | | | |
| 074 ADME RANGE | 1992-1993 | | | 40 | | | | |

* Multiple Dose - little or no accumulation observed. P = patient; S = subject; M = male; F = female

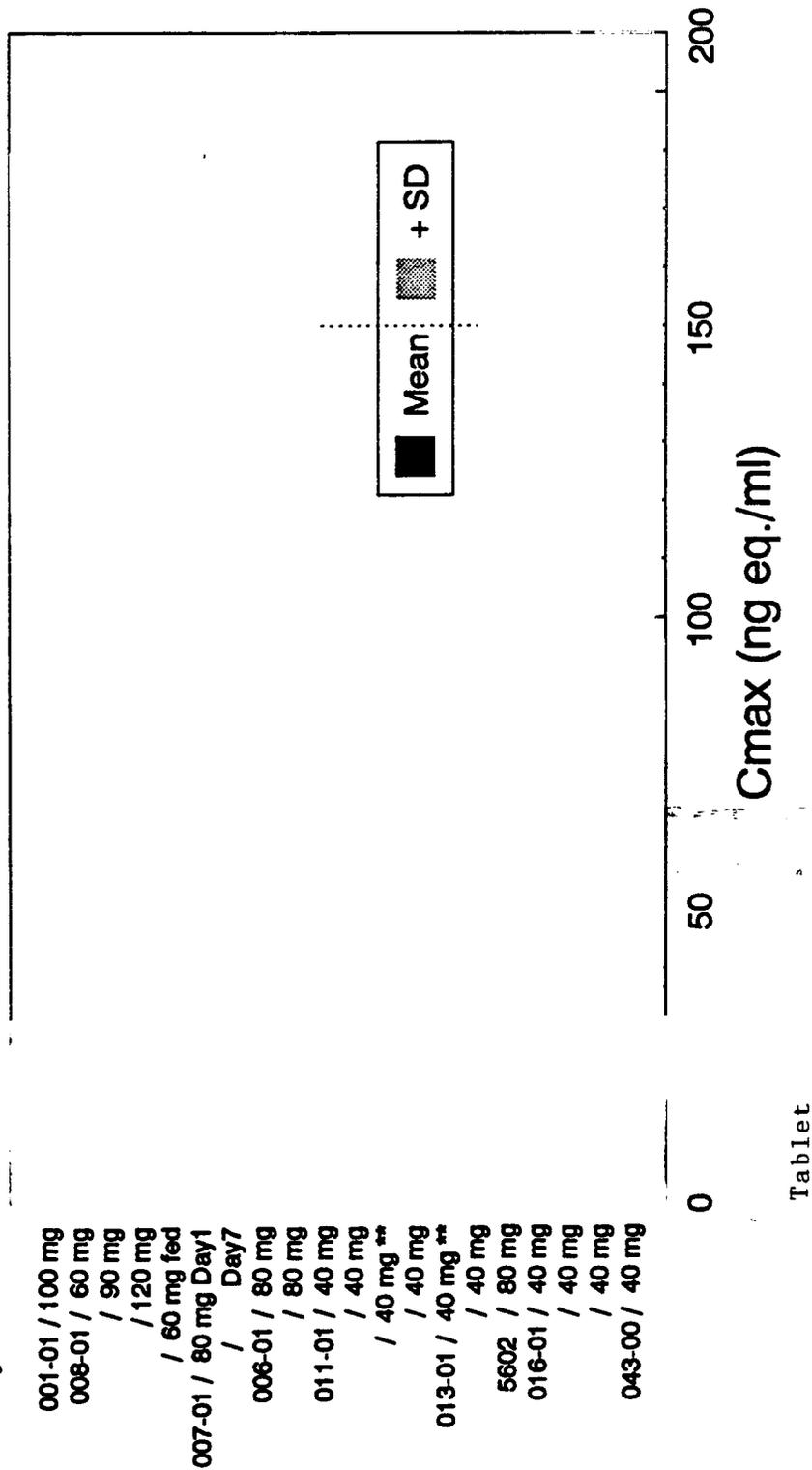
AUC OF TOTAL INHIBITORS IN HUMAN STUDIES

Simvastatin: Data Normalized to 40 mg



Cmax of Total Inhibitors in Human Studies Simvastatin: Data Normalized to 40 mg

Study No. / Dose Administered



Tablet

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

These copies are OFFICIAL FDA Copies
not desk copies.

June 25, 1998



Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Sobel:

**NDA 19-766/S-026: ZOCOR® (Simvastatin)
General Correspondence**

Reference is made to the above Supplemental New Drug Application (SNDA). Reference is also made to an annotated label, dated June 23, 1998, and submitted for review on June 24, 1998, and a telephone conversation between Dr. David Orloff, Food and Drug Administration (FDA), and Dr. Charles Hyman, Merck Research Laboratories (MRL), on June 24, 1998, during which additional changes to the annotated label submitted were discussed. By this letter, MRL is resubmitting for your review an updated annotated label for ZOCOR that incorporates those additional changes discussed with Dr. Orloff on June 24, 1998.

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 further questions or need additional information, please contact Charles L. Hyman, M.D. (610) 397-2850 or, in my absence, Robert E. Silverman, M.D., Ph.D. (610) 397-2944.

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

Margo E. Herron
for Charles L. Hyman, M.D.
Charles L. Hyman, M.D.
Director
Regulatory Affairs

Hand Delivered by Ms. Margo Herron

Desk Copies (hand delivered):

Dr. David Orloff, HFD-510, Rm. 14B-04
Ms. Margaret Simoneau, HFD-510, Rm. 14B-04

APPEARS THIS WAY
ON ORIGINAL

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

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

June 23, 1998



Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Sobel:

**NDA 19-766/S-026: ZOCOR® (Simvastatin)
General Correspondence**

Reference is made to the above Supplemental New Drug Application (SNDA). Reference is also made to telephone conversations between Dr. David Orloff, Food and Drug Administration (FDA), and Dr. Charles Hyman, Merck Research Laboratories (MRL), on June 17 and 18, 1998, regarding changes to be made to the CLINICAL PHARMACOLOGY, WARNINGS, AND DOSAGE & ADMINISTRATION sections of the ZOCOR label as they pertain to this supplement for the 80 mg dose. Reference is further made to Dr. Elizabeth Barbehenn's (FDA) requested changes to the *CNS Toxicity, Carcinogenesis, Mutagenesis, Impairment of Fertility, and Pregnancy* subsections of the PRECAUTIONS section of the label that were submitted by MRL on April 24, 1998, and discussed with and accepted by Dr. Barbehenn in a telephone conversation with Dr. Hyman on April 28, 1998. By this letter, MRL is submitting for your review an annotated label for ZOCOR that incorporates those changes discussed with Dr. Orloff, and those accepted by Dr. Barbehenn.

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..

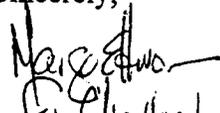
S. Sobel, MD, Director
NDA 19-766/S-026: ZOCOR
June 23, 1998
Page Two

APPEARS THIS WAY
ON ORIGINAL

If you have further questions or need additional information, please contact Charles L. Hyman, M.D. (610) 397-2850 or, in my absence, Robert E. Silverman, M.D., Ph.D. (610) 397-2944.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL


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

Hand Delivered by Ms. Margo Herron

Desk Copies (hand delivered):

Dr. David Orloff, HFD-510, Rm. 14B-04

Ms. Margaret Simoneau, HFD-510, Rm. 14B-04

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APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

DESK COPY

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

May 27, 1998

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



Dear Dr. Sobel

**NDA 19-766/S-026: ZOCOR™(Simvastatin)
GENERAL CORRESPONDENCE**

Reference is made to the Supplemental New Drug Application cited above and to a telephone conversation on May 25, 1998 between Ms. Margaret Simoneau, Food and Drug Administration (FDA) and Dr. Charles Hyman, Merck Research Laboratories (MRL) in which Ms. Simoneau requested MRL provide copies of the product label on diskette to facilitate Dr. Robert Shore's review of S-026.

Attached as requested, is one (1) diskette containing the following five files:

- #1. 80MGPRI.DOC
This is a copy of the annotated label as originally submitted on August 4, 1997.
- #2. 80MGCRT.DOC
This is a copy of the clean running text as originally submitted on August 4, 1997.
- #3. PRECLIN6.DOC
This file contains the changes to the CNS Toxicity, Carcinogenesis, Mutagenesis, Impairment of fertility, and of the PRECAUTIONS section of the label that was reviewed and approved by Dr. Barbehenn as of April 24, 1998. Annotated format.
- #4. PRECLIN7.DOC
This file contains the changes to the CNS Toxicity, Carcinogenesis, Mutagenesis, Impairment of fertility, and Pregnancy sections of the PRECAUTIONS section of the label that was reviewed and approved by Dr. Barbehenn as of April 24, 1998. Clean Running Text format.
- #5. README.DOC
This short memo is readme.doc.

APPEARS TO BE ON ORIGINAL
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APPEARS TO BE ON ORIGINAL
APPEARS TO BE ON ORIGINAL

Letter to: S. Sobel, M.D.
NDA 19-766/S-026 ZOCOR™
May 27, 1998
Page Two

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..

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

Sincerely,



Charles L. Hyman
Director
Regulatory Affairs

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ON ORIGINAL

Attachment: 1 Diskette

Federal Express #1

(2) Desk Copies with diskettes: Ms. Magaret Simoneau, HFD-510, Rm 14B04

q:murakami\zocor\disks.doc

APPEARS THIS WAY
ON ORIGINAL

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

April 24, 1998

DESK COPY



Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Via Fax: 301.443.9282 (with attachments)

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Sobel:

NDA 19-766/S-026: ZOCOR™ (simvastatin)

Reference is made to the above referenced Supplemental New Drug Application (SNDA). Reference is also made to the fax sent by the Food and Drug Administration (Agency) to Merck Research Laboratories (MRL) on April 17, 1998, in which the Agency proposed changes to the *CNS Toxicity, Carcinogenesis, Mutagenesis, Impairment of Fertility, and Pregnancy* subsections of the PRECAUTIONS section of the label. By this letter, MRL is providing our response to these label changes.

Attached are the relevant sections of the label which have been annotated to incorporate the Agency's suggested changes. In addition, MRL proposes some editorial changes and corrections which are identified as such by annotation.

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 further questions or need additional information please contact Charles L. Hyman, M.D. (610. 397.2850) or, in my absence, Robert E. Silverman, M.D., Ph.D. (610.397.2944).

Sincerely,

A handwritten signature in black ink, appearing to read 'Hyman', written over a circular stamp or mark.

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

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

DESK COPY

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

March 26, 1998

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Via Fax: 301.443.0072

Dear Dr. Sobel:

**NDA 19-766/SE-026: ZOCOR® (Simvastatin)
Response to Request for Information**

Reference is made to the above Supplemental New Drug Application and also to a telephone request from Dr. Elizabeth Barbehenn, Food and Drug Administration Pharmacologist, through Ms. Margaret Simoneau on March 11, 1998, regarding the data used for making comparative exposure statements that appear in the ZOCOR label in the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection of the Precaution section. By this letter, Merck Research Laboratories (MRL) is providing the requested data and reference studies.

The AUC data for rats and the multiples of human exposure are provided in the table below. The data for the AUC in rats given 50 and 100 mg/kg/day of simvastatin were generated in Study TT #90-189-0, and Table III from this study report listing these data is attached (Attachment 1). The data for the AUC in rats given 25 mg/kg/day of simvastatin were generated for male rats only in Study TT #91-116-0, and Table 6 from this study report listing these data is provided in Attachment 2. AUC for 25 mg/kg/day was also derived by dividing values obtained from 50 mg/kg/day by 2. In addition, the mean AUC for dogs receiving 10 mg/kg/day of simvastatin was determined in Study TT #87-077-0 to be 1074.5 ng-h/ml, and Table 9 from this study report listing these data is provided in Attachment 3.

| 24-Hour AUC of Total Inhibitors in Rats Receiving Simvastatin (ng eq-hr/ml) | | | |
|--|--------------|----------------|--|
| | <u>Males</u> | <u>Females</u> | <u>Multiple of Human Exposure*</u> |
| 100 mg/kg/day | 9,563 | 15,618 | 94-153X |
| 50 mg/kg/day | 4,418 | 13,645 | 43-134X |
| 25 mg/kg/day** | 2,209 | 6,822 | 22- 67X |

*based upon a 24-AUC in man of 102 ng eq-hr/ml after a 40 mg dose (Protocol 043; Attachment 4).

**based upon a) AUC for 50 mg/kg/day divided by 2; and b) in a separate study using male rats only (TT #91-116-0) administered 25 mg/kg/day of simvastatin for 14 days the AUC was 2436 ng eq-hr/ml.

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ON ORIGINAL

Letter to: S. Sobel, MD
NDA 19-766/SE-026
March 26, 1998
Page Two

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..

We hope the information provided herein satisfactorily addresses your questions. If you have further questions or need additional information please contact 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

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ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Attachments - 4

APPEARS THIS WAY
ON ORIGINAL

Certified No.: P 963 205 899
Desk Copy: Certified No.: P 963 205 900 Dr. Elizabeth K. Barbehenn, HFD-510
Certified No.: P 967 678 533 Ms. Margaret Simoneau, HFD-510

chl\fh hark\zoc\fa018L.doc

APPEARS THIS WAY
ON ORIGINAL

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

January 23, 1998

DESK COPY

Dr. H. W. Ju
Division of Scientific Investigations Clinical Branch
HFD-344, Room 125
Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855



Dear Dr. Ju:

NDA 19-766 / SE2-026 ZOCOR™ (Simvastatin) General Correspondence

Reference is made to the above Supplemental New Drug Application submitted on August 4, 1997. Reference is also made to a response to Dr. H. W. Ju's request for additional information concerning sites 117-008 (Dr. Carlos Dujovne) and 117-021 (Dr. Evan Stein) submitted on January 16, 1998.

Merck Research Laboratories (MRL) has identified a documentation processing error in Dr. Stein's data contained in Volume 2 of this submission. Three pages were inadvertently not included in the List of Subjects Reported with an Adverse Event in the Adverse Event Section. The omitted three pages contain Verbatim Terms for the Simvastatin 40 mg/day treatment group. The original submission contained only the Simvastatin 80 mg/day treatment group under Verbatim Terms.

Please find attached the missing pages from Dr. Stein's data from Volume 2 of the January 16, 1998 submission. The pages are numbered 82.1, 82.2 and 82.3. Please insert behind the Tab labeled Adverse Experiences, 117-021 after page 82.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request 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.

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

Sincerely,

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

APPEARS THIS WAY
ON ORIGINAL

Q:CATLMSE2-026

Attachment

Federal Express #1

Desk Copy: Official File NDA 19-766/SE2-026: ZOCOR™ (Simvastatin), HFD-510, cover letter only,

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

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not desk copies.**

January 16, 1998



Dr. H. W. Ju
Division of Scientific Investigations Clinical Branch
HFD-344, Room 125
Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855

Dear Dr. Ju:

**NDA 19-766/SE2-026
ZOCOR™ (Simvastatin)**

RESPONSE TO REQUEST FOR INFORMATION

Reference is made to the above Supplemental New Drug Application submitted on August 4, 1997. Reference is also made to telephone conversations between Dr. H. W. Ju, Division of Scientific Investigations (DSI) and Dr. Charles L. Hyman, Merck Research Laboratories (MRL) on January 5 and 6, 1998. During these conversations, Dr. Ju stated that the FDA intended to perform inspections at sites 117-008 (Dr. Carlos Dujovne) and 117-021 (Dr. Evan Stein) and requested additional information in preparation for these visits.

With this letter, MRL is providing the requested additional information. This submission consists of two volumes. Volume 1 contains data concerning Dr. Dujovne's site, 117-008 and Volume 2 contains data concerning Dr. Stein's site, 117-021. A copy of the original protocol and copies of the cover letters for each protocol amendment for Protocol 117 are located at the beginning of each volume followed by site specific information as follows:

- Form 1572 for the principal investigator.
- The number of subjects enrolled, and the number completing the study.
- A list of all subjects who were discontinued from the study and reason.
- A list of all subjects reported with an adverse event, and the adverse event.
- A list of subjects reported as protocol violators, and nature of violation.
- For Site 008, the CRF of the 1st, 10th, 20th, and 30th subject enrolled.
- For Site 021, the CRF of the 1st, 10th, 30th, and 45th subject enrolled.

Dr. H. W. Ju
NDA 19-766/SE2-026
ZOCOR™ (Simvastatin)
RESPONSE TO REQUEST FOR INFORMATION
Page 2

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We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request 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.

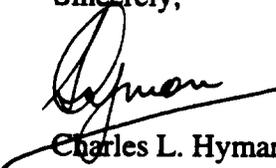
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ON ORIGINAL

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

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



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

Federal Express #1

APPEARS THIS WAY
ON ORIGINAL

Desk Copies (cover letter only)

FDA File: FDA 19-766 / SE2-026: ZOCOR™ (Simvastatin), Dr. Sobel,
HFD-510, Rm. 14B-04

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APPEARS THIS WAY
ON ORIGINAL

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

December 16, 1997

DESK COPY

Dr. H. W. Ju
Division of Scientific Investigations Clinical Branch
HFD-344, Room 125
Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855



Fax: 301.594.1204

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Ju:

**NDA 19-766/SE2-026
ZOCOR™ (Simvastatin)**

RESPONSE TO REQUEST FOR INFORMATION

APPEARS THIS WAY
ON ORIGINAL

Reference is made to the above Supplemental New Drug Application submitted on August 4, 1997 and to a telephone conversation with Dr. Charles L. Hyman on December 12, 1997. During this conversation you requested a list of all Phase III studies included in the above cited supplement, along with a corresponding listing of study sites and primary investigators. In addition you requested the following information for each of those sites and investigators: study site number, number of patients entered, and number of patients completed.

APPEARS THIS WAY
ON ORIGINAL

By this letter we are providing you with the requested information. The only Phase III study included in this supplement was Protocol #117, "A Multicenter, Double-Blind, Two Arm Parallel Study to Evaluate the Efficacy and Safety of High Dose (80mg) Simvastatin in Patients With Hypercholesterolemia." Please note that the United States sites are listed first followed by the international sites.

APPEARS THIS WAY
ON ORIGINAL

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

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

A handwritten signature in cursive script, appearing to read 'C. Hyman', written over a horizontal line.

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

APPEARS THIS WAY
ON ORIGINAL

Federal Express #1

Desk Copy: Ms. Margaret Simoneau, HFD-510, Rm. 14B-04, Federal Express #2

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- **Primary Investigator/Address**—Identifies the name and address of the primary study investigator and study site/facility at which the study was conducted.

If the original primary investigator has been replaced, that primary investigator's name is followed by a slash (/) and the replacement primary investigator's name.

- **Protocol-Study Number (XXX-XXX)**—As indicated.

A dagger (†) next to the protocol-study number indicates that a Worldwide Clinical Quality Assurance Resources (WCQAR) audit was performed by MRL for that study at the investigator's site.

- **Study Title**—As indicated.
- **Number Subjects/Patients Entered**—Indicates the number of subjects/patients entered at that site by the in-house case report form (CRF) cutoff date.
- **Start Date**—The first date subjects/patients received study drug.
- **In-House Cutoff Date**—The date the last CRF was received for inclusion in the CSR. Any exceptions are indicated by a footnote.

APPEARS THIS WAY
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APPEARS THIS WAY
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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

December 4, 1997

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:

NDA 19-766 / SE2-026: ZOCOR™ (Simvastatin)

Safety Update Report

Reference is made to the above supplemental New Drug Application (sNDA) submitted August 4, 1997. Submitted with this letter is the Safety Update Report (SUR) for this supplemental application. An electronic version of this report will be submitted within 10 working days.

This SUR provides updated safety information for simvastatin 80 mg/day for the treatment of hypercholesterolemia subsequent to the sNDA submitted on August 4, 1997. This period extends the Safety profile for approximately 6 months. The SUR provides new clinical and laboratory safety data a total of 765 patients with hypercholesterolemia and cumulative clinical and laboratory safety data for 1146 patients. All safety data available as of the date of September 19, 1997 are included. Special safety evaluations of the effects of simvastatin on muscle, liver, testosterone, gonadotropins, and cortisol are included. An additional section has been included on ophthalmologic findings and the potential *in vivo* effect of simvastatin 80 mg/day on cytochrome P450 3A4 activity is also presented.

The safety data presented in this SUR support the overall favorable safety and tolerability profile of simvastatin 80 mg/day presented in the sNDA and the proposed product label.

The listing tables referenced in this document, will be included in the electronic submission, but due to their size they will not be supplied in this hard copy submission.

Solomon Sobel, M.D. - Director
NDA 19-766 / SE2-026: ZOCOR™ (Simvastatin)
Page 2

APPEARS TO BE
ON ORIGINAL

We consider the filing of this Safety Update Report to be a confidential matter, and request 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.

APPEARS TO BE
ON ORIGINAL

Please direct questions or need for additional information to Charles L. Hyman, M.D. (610/397-2850) or, in my absence Robert E. Silverman, M.D., Ph.D. (610/397-2944).

Sincerely yours,



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

APPEARS TO BE
ON ORIGINAL

Attachments

Federal Express #1

Desk Copies w/attachments: Ms. Margaret Simoneau, CSO, HFD-510, Rm. 14B-04
Federal Express #2

Dr. David Orloff, HFD-510, Rm. 14B-04
Federal Express #3

APPEARS TO BE
ON ORIGINAL

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

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

August 15, 1997

DESK COPY



Solomon Sobel, M.D., Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Sobel:

NDA 19-766/S-026, ZOCOR™
(Simvastatin)

Reference is made to the above Supplemental New Drug Application (SNDA) submitted on August 4, 1997, and a briefing between Merck Research Laboratories (MRL) and CDER representatives on July 16, 1996, concerning MRL's Clinical and Regulatory Information Strategic Project (CRISP).

On July 16, 1996, MRL presented to FDA a summary of a new clinical data collection, analysis and reporting system, "CRISP". The above noted SNDA included the initial submission to the Agency of data from clinical studies that utilized the CRISP system. Background information is attached on several issues which arose in this initial use of the CRISP system. MRL would like to request a meeting with appropriate Agency representatives to discuss these issues and the actions taken by MRL in response to these issues. MRL participants from Regulatory Affairs, Clinical Research, Clinical Biostatistics, Research Information Systems and Clinical Quality Assurance are prepared to elaborate on the material summarized in the attachment. We would suggest that Agency participants include representation from the Division of Endocrine and Metabolic Drug Products, the Office of Compliance and the Office of Information Technology.

Biometrics

Dr. Silverman will contact Ms. Simoneau in the next two weeks to pursue the scheduling and format for the requested meeting.

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.

9/5/97

21 August Solomon Sobel

J (Compliance)

Glucos

Study 26 (Supplement)

If you have any questions or need additional information please contact Robert E. 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

APPEARS THIS WAY
ON ORIGINAL

mcs/q/tr/472

Attachment

Federal Express #1

Desk Copy: Ms. Margaret Simoneau, HFD-510, Rm. 14B-04, Federal Express #1
Dr. David Orloff, HFD-510, Rm. 14B-19, Federal Express #1
Dr. Bette Barton, HFD-344, MPN1/Rm. 125, Federal Express #2
Mr. Thomas Ju, HFD-344, MPN1/Rm. 125, Federal Express #2
Dr. David Lepay, HFD-340, MPN1/Rm. 103, Federal Express #3
Mr. Gurston Turner, HFD-344 MPN1/Rm. 125, Federal Express #2
Dr. David Isom, HFD-001, WOC2 6049, Federal Express #4
Mr. Paul Motise, HFD-325, MPN1/Rm. 272, Federal Express #5

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

DESK COPY

April 6, 1998

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



MERCK
Research Laboratories

Dear Dr. Sobel:

**Supplemental New Drug Application: NDA 19-766/SCF-028
ZOCOR™ (Simvastatin)**

Reference is made to the above Supplemental New Drug Application (SNDA) submitted on August 4, 1997.

Merck Research

In addition, reference is made to a letter to the FDA dated December 15, 1995, which documented an agreement reached between the Agency and MRL in reference to a waiver of the requirement for data from the 12 month market container stability studies since the 80 mg formulation is an exact weight multiple of the currently marketed 40 mg formulation. MRL provides six month market container stability data with the initial submission of the simvastatin - 80 mg SNDA (SCF-028).

In accordance with the previous communications, MRL is providing, as an attachment to this letter the stability update to the Tablet ZOCOR™ SNDA (SCF-028) for the 80 mg strength tablet. Attachment I contains the 12 month market container stability data for Tablets ZOCOR™ 80 mg, and Attachment 2 contains the Statistical Evaluation of the Marketed Container Stability Studies.

Pursuant to 21 CFR 314.70(a), a complete field copy of this [amendment/supplement] has been submitted to the FDA Philadelphia District Office.

As required by Section 306(k)(1) of the Generic Enforcement Act [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.

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.

APPEARS THIS WAY
ON ORIGINAL

Solomon Sobel, M.D. - Director
NDA 19-766/SCF-028
ZOCOR™ (Simvastatin)
Page 2

Please direct questions or need for additional information 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

q:\robinson\murakami\19766ltr

APPEARS THIS WAY
ON ORIGINAL

Attachment
Federal Express #1

Desk Copies: Ms. Margaret Simoneau, HFD-510, Rm. 14B-04, Federal Express #1 (w/o att)
Dr. David Orloff, HFD-510, Rm. 14B-04, Federal Express #1 (w/o att)
Dr. William Berlin, HFD-510, Rm. 14B-31, Federal Express #1 (w/att)

Desk Copy: Philadelphia District Office
ATTN: Ms. Debra L. Pagano
U.S. Custom House, Room 900
2nd & Chestnut Street
Philadelphia, PA 19106-2973
Federal Express #2

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

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

DESK COPY

November 19, 1997



Solomon Sobel, M.D., Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Sobel:

Supplemental New Drug Application: NDA 19-766/S-028
ZOCOR™ (Simvastatin)

Reference is made to the above Supplemental New Drug Application NDA 19-766/S-028 originally submitted on August 4, 1997.

As a result of this change, Merck Manufacturing Division Cramlington, U.K., will be the only release testing site for Tablets ZOCOR™ 80 mg.

Pursuant to 21 CFR 314.60(c), a complete field copy of this amendment has been submitted to the FDA Philadelphia District Office.

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [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.

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.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions or need additional information please contact Robert E. 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

mcs/q/tr/515

Attachment

Federal Express #1

Desk Copy: Dr. William Berlin, HFD-510, Rm. 14B-45, Federal Express #1
Ms. Margaret Simoneau, HFD-510, Rm. 14B-04, Federal Express #1

Philadelphia District Office, Attn.: Ms. Debra L. Pagano
U.S. Custom House Room 900, 2nd & Chestnut Streets
Philadelphia, PA 19106-2973
Federal Express #2

APPEAR AS THIS WAY
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ON ORIGINAL

TABLETS ZOCOR® (simvastatin) 80 MG

This is to provide notification of withdrawal of the following facility as an alternate site for release testing for simvastatin tablets, 80 mg:

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ON ORIGINAL

Release testing for simvastatin tablets, 80 mg will be performed at the following facility:

Merck Manufacturing Division
Shotton Lane, Cramlington
Northumberland, UK, NE23 9JU

Please note that Covance Laboratories, Ltd. will store and conduct the testing of the market container stability study samples of simvastatin tablets, 80 mg.

APPEARS THIS WAY
ON ORIGINAL

SC 2-026 BC

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

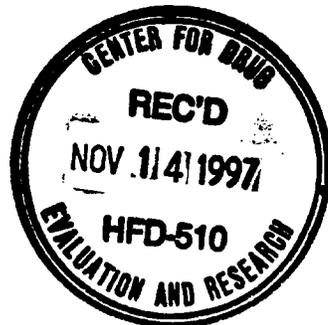
Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

These copies are
OFFICIAL FDA Copies
not desk copies.

November 13, 1997



Solomon Sobel, M.D., Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. Sobel:

NDA 19-766/S-026: ZOCOR™
(Simvastatin)

Reference is made to the above Supplemental New Drug Application (SNDA) submitted on August 4, 1997 and a telephone conversation between Dr. Silverman and Dr. Berlin during which the Agency and Merck Research Laboratories (MRL) discussed the possibility of a waiver from the requirement for an Environmental Assessment for the above noted SNDA.

By attachment, MRL is providing, herein, a request for categorical exclusion under 21CFR25.31(b) from the requirement for an Environmental Assessment.

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 E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

| |
|---|
| REVIEWS COMPLETED |
| CSO ACTION: |
| <input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO |
| CSO INITIALS _____ DATE _____ |

Sincerely,

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

Noted /S/ May 18, 1998

mcs/q/tr/509

Attachment

Federal Express #1

Desk Copy: Dr. William Berlin, HFD-520, Room 14B-31, Federal Express #2

Ms. Margaret Simoneau, HFD-510, Room 14B-04, Federal Express #1

noted /S/ 97

I. Summary

F. Environmental Assessment - Categorical Exclusion

F. Environmental Assessment - Categorical Exclusion

F.1. Date

November 1, 1997

F.2. Name of Applicant

Merck Research Laboratories
Merck and Co., Inc.

F.3. Address

Sumneytown Pike
West Point, PA 19486

F.4. Description of Proposed Action

F.4.a. Requested Action

Merck & Co., Inc. is filing a Supplemental New Drug Application requesting the approval of ZOCOR® Tablets, 80 mg. Drug substance manufacture will take place at the Merck Manufacturing Division facilities located in

Drug product manufacture will take place at the Merck Manufacturing Division facility located in _____ and drug product packaging will take place at the Merck Manufacturing facility located in _____

Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment

I. Summary

F. Environmental Assessment - Categorical Exclusion

F.4.a. Requested Action - Categorical Exclusion (Cont.)

under 21 CFR §25.31(b). The production of ZOCOR®
Tablets, 80 mg 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
part per billion (ppb). To the best of the firm's
knowledge no extraordinary circumstances exist in regards
to this action.

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