CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-766/S052

ADMINISTRATIVE DOCUMENTS

Division of Metabolic & Endocrine Drug Products

Labeling Review

Application Number: 19-766/S-052

Name of Drug: Zocor (simvastatin)Tablets

Sponsor: Merck

Submission Date: November 30, 2001

Background and Summary:

This supplement provides for changes to the CLINICAL PHARMACOLOGY section of the Zocor package insert, which describe the influence of total cholesterol, LDL-C, Apo B, HDL-C, Apo A-1 and triglyceride levels on the risks of cardiovascular disease.

This change was added to last approved labeling supplements, S-45 and S-053, which were approved on November 14, 2001 (Package Identifier # 7825441). Supplement–045 provides for revisions to the **WARNINGS**, *Skeletal Muscle* subsection, **PRECAUTIONS**, and **ADVERSE REACTIONS** sections of the Package Insert. Supplement–053 provides for replacement of the previous version of the National Cholesterol Education Program (NCEP) Guidelines Table 3 with the updated NCEP Adult Treatment Panel (ATPIII) Guidelines Table 5 and an additional paragraph in the **INDICATIONS AND USAGE** section of the package insert.

Review:

In **CLINICAL PHARMACOLOGY** section, the first paragraph, second and third sentences were changed to read as follows:

Epidemiological studies have established that elevated plasma levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (Apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of high-density lipoprotein cholesterol (HDL-C) and its transport complex, Apo A-I, are associated with decreased cardiovascular risk. High plasma triglycerides (TG) and cholesterol-enriched TG-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis.

Conclusion:

The proposed draft label (Package Identifier #782544X), submitted November 30, 2001, was deemed acceptable by the reviewing team and an electronic labeling review was completed on March 11, 2002. The Agency will issue an approval action on this supplement.

Reviewed by: M.A. Simoneau, R.Ph., Regulatory Project Manager/EG 3/19/02
(See appended electronic signature page)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Margaret Simoneau
3/20/02 03:02:10 PM
CSO

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ON ORIGINAL

WITHHOLD 1 PAGE (S)

Draft

Labeling

EXCLUSIVITY SUMMARY for NDA # 19-766 SUPPL # S-052
Trade Name Zocor Generic Name Simvastatin
Applicant Name Merck & Co., Inc. 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 /_X__/

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

      If yes, what type(SE1, SE2, etc.)? SE8

   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 /_X__/ 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 /_X__/

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?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 /_X_/ NO /___/

If yes, NDA # 19-766 Drug Name Zocor

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 9 (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 /___/

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

NDA #

NDA #

NDA #

2. Combination product.

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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 /___/

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 9:**

(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 #

Investigation #2, Study #

Investigation #3, Study #

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 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:

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

(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 /___/

Investigation #3 YES /___/ NO /___/

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 #

(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 #__, Study #

Investigation #__, Study #

Investigation #__, Study #

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?

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: _____

_____

_____

M. Simoneau,R.Ph. October 1, 2001
Signature of Preparer Date
Title: Regulatory Project Manager

Mary Parks,MD, Medical Team Leader October 1, 2001
Date

David Orloff, MD
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

APPEARS THIS WAY,
ON ORIGINAL

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

MESSAGE CONFIRMATION

08/17/01 07:49
ID=FDA CDER DMEDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
08/17	00'45"	914843442516	CALLING	03	OK	0000

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08/17/01 07:47 FDA CDER DMEDP → 914843442516 NO.001 P01

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 16, 2001

To: Michael Elia, Ph.D., DABT	**From:** Margaret Simoneau
Company: Merck & Co., Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 484-344-2516	**Fax number:** (301) 443-9282
Phone number: 484-344-3180	**Phone number:** (301) 827-6411

Subject: NDA 19-766/S-052 Labeling Comments

Total no. of pages including cover: 3

Comments:

Simvastatin

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Bonnie Goldmann, M.D.
Vice President, Regulatory Affairs, Domestic
Merck & Company, Inc.
Sumneytown Pike, BLA-20
P.O. Box 4
West Point, PA 19486-0004

MAY 20 2002

Invoice Enclosed

RE: Application Fee for NDA 19-766, Zocor (simvastatin), Supplement-052

Dear Dr. Goldmann:

This communication includes an invoice (Attachment A) for an application fee for fiscal year (FY) 2001 under the user fee provisions of the Federal Food, Drug, and Cosmetic Act (the Act)[1] for supplement 052 to new drug application (NDA) 19-766 Zocor (simvastatin).

I. Background Information for Supplement 052.

The Division of Metabolic and Endocrine Drug Products (DMEDP) received a supplement —— to NDA 19-766 on December 4, 2000, requesting labeling changes to the Clinical Pharmacology, ———————— sections of the Zocor package insert. DMEDP administratively separated the submission into two supplements (supplement — and supplement 052). ————————

The changes to the Clinical Pharmacology section of the Zocor package insert, which describe the influence of total cholesterol, LDL-C, Apo B, HDL-C, Apo A-1 and triglyceride levels on the risks of cardiovascular disease, were administratively separated to supplement 052. Merck & Company, Inc. (Merck) submitted the labeling changes but did not submit the fee for a supplement that requires clinical data for approval for supplement — and supplement 052.

II. When is a Supplement Subject to a Fee?

Under section 736(a)(1)(A)(ii) of the Act, a fee is required for "a supplement for which clinical data (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness are required." The definition of *clinical data* for purposes of assessing user fees can be found in the draft guidance for industry on *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*

[1] Section 736(a)(1) of the Act (21, U.S.C. 379h(a)(1)).

(guidance document), dated December 2000.[2] The pertinent portions of the guidance document that define clinical data state:

> User fees will be assessed for original applications (NDAs or BLAs) and supplements containing the following types of clinical data required to form the primary basis for approval:
>
> - study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials; or
>
> - reports of comparative activity (other than bioequivalence and bioavailability studies), immunogenicity, or efficacy, where those reports are necessary to support a claim of comparable clinical effect.
>
> For purposes of assessing user fees, *clinical data* do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication, or warning to the labeling).
>
> Supplements to new drug applications based solely on bioequivalence studies or studies of bioavailability of a drug are not considered to contain clinical data for purposes of assessing user fees, even if the studies include clinical endpoints.

III. Should Supplement 052 be Assessed a Fee?

We have reviewed our files and consulted with DMEDP. Labeling supplement 052, approved March 21, 2002, provided for changes to the Clinical Pharmacology section of the Zocor package insert labeling, describing the influence of total cholesterol, LDL-C, Apo B, HDL-C, Apo A-1 and triglyceride levels on the risks of cardiovascular disease. The labeling changes approved in supplement 052 were based upon the four published articles submitted, as noted in the medical review for this supplement. The published studies fit the definition of *adequate and well controlled* as described in 21 CFR 314.126, and, as a result, fit the user fee definition of clinical data for user fee purposes. Therefore, a user fee should be assessed because clinical data with respect to safety or effectiveness were required for approval for supplement 052.

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[2] Available on the Internet at www.fda.gov/cder/pdufa/default.htm under Guidances.

IV. Assessment of Fees.

The enclosed invoice is for the FY 2001 application fee ($154,823) for a supplement (S-052) that requires clinical data for approval. **Payment is due within 30 days of the date of the invoice.** Instructions for payment are included in Attachment B.

If you have any questions concerning this matter or other user fee questions, please contact Michael Jones or Beverly Friedman at:

Center for Drug Evaluation and Research
Food and Drug Administration, HFD-5
5600 Fishers Lane
Rockville, Maryland 20857
301-594-2041
FAX: 301-827-5562

e-mail: jonesm@cder.fda.gov
friedmanb@cder.fda.gov

We appreciate your continued cooperation and thank you in advance for your prompt payment.

Sincerely,

/S/

Helen S. Horn, Acting Director
Office of Financial Management

Enclosures

Attachment A – Action Invoice
Attachment B – Payment Instructions

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ON ORIGINAL

HFD-5, Merck User Fee File
HFD-5, M.Jones
HFM-110, C.Vincent
HFA-120 D.Simms
HFA-102, S.Farran
HF-20, F.Claunts
HFD-560, P.Simoneau
HFD-560, E.Galliers

Drafted, 4/10/2002, M.Jones
Reviewed, 4/10/2002, B.Friedman
Revised 4/11/2002, M.Jones
Revised 4/19/2002, M.Jones
Edited 4/22/2002, F.Purdie
Revised 4/23/2002, M.Jones
Reviewed 4/25/2002, J.Axelrad
Concur w/ minor edit 4/26/2002, HFD-510
Final prepared, 4/29/2002, M.Jones

/S/ 4.29.2002
/S/ 5/6/02

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FDA FOOD AND DRUG ADMINISTRATION

INVOICE

Bill Number:

Bill Date: 20-MAY-2002

Make remittance payable to and mail to:

FOOD AND DRUG ADMINISTRATION
P.O. BOX 360909
Pittsburgh, PA 15251-6909

Payments sent by private courier must be addressed to:

FOOD AND DRUG ADMINISTRATION (360909)
Mellon Client Service Center Rm 670
500 Ross Street
Pittsburgh, PA 15262-0001

Firm ID: 37904

Firm: MERCK RESEARCH LABORATORIES DIV MERCK CO INC
POST OFFICE BOX 4
SUMNEYTOWN PIKE BLA 20
WEST POINT PA 19486-0004

ATTN: BONNIE GOLDMAN, M.D.

TOTAL APPLICATION AMOUNT DUE: $ 154,823

Payment must be received by the U.S. Food and Drug Administration within 30 days of the date of this invoice in U.S. dollars, by check, bank draft, or U.S. Postal money order payable to the order of the U.S. Food and Drug Administration. Any check or bank draft should be drawn on or payable through U.S. financial institutions located in the United States.

If full payment is not received within 30 days of the date of this invoice, an interest rate of 11.75% will be charged. In addition, delinquent invoices will be assessed a $20 administrative fee for each full 30 day period that the account remains outstanding. A 6% late payment penalty fee also will be charged as stated in 45 CFR Subtitle A, Section 30.13.

A receipt will be issued upon request. The invoice will not be considered paid until payment has been cleared and the amount received by the U.S. Food and Drug Administration.

For further information concerning this invoice, contact: Beverly Friedman at (301) 594-2041.

*** See ATTACHMENT B for payment instructions . . . . .**