Center for Drug Evaluation and Research

Approval Package for:

Application Number:
NDA 19-766/S025

Trade Name: Zocor Tablets

Generic Name: Simvastatin

Sponsor: Merck & Company, Inc.

Approval Date: December 2, 1997
# Reviews / Information Included in this NDA Review

<table>
<thead>
<tr>
<th>Review Type</th>
<th>Included</th>
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<tr>
<td>Approval Letter</td>
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<td>Labeling</td>
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<td>Medical Review(s)</td>
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<td>Chemistry Review(s)</td>
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<td>Pharmacology Review(s)</td>
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<td>Statistical Review(s)</td>
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<td>Microbiology Review(s)</td>
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<tr>
<td>Clinical Pharmacology/ Biopharmaceutics Review(s)</td>
<td></td>
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<tr>
<td>Administrative/Correspondence Document(s)</td>
<td>X</td>
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</table>
APPLICATION NUMBER:
NDA 19-766/S025

APPROVAL LETTER
Merck Research Laboratories  
Attention: Robert E. Silverman, M.D., Ph.D.  
Sumneytown Pike  
West Point, PA 19486  

Dear Dr. Silverman:


The User Fee goal date for this application is January 29, 1998.

The supplemental application provides for the addition of a test method and specification for a in simvastatin drug substance.

We have completed the review of this supplemental application and it is approved.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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

If you have any questions, please contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6430.

Sincerely yours,

Stephen K. Moore, Ph.D.
Chemistry Team Leader I, DNDC II
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

12-2-97
NDA 19-766/S-025
Page 2

cc:
Original NDA 19-766
HFD-510/Div. Files
HFD-510/CSO/M. Simoneau
HFD-510/E.Barbehenn/B.Berlin/S.Moore
HFD-820/ONDC Division Director
HFD-92/DDM-DIAB
DISTRICT OFFICE

Drafted by: Mas/November 18, 1997/19766.025
final: Mas 12/1/97

APPROVAL (AP)
<table>
<thead>
<tr>
<th>CHEMISTS REVIEW</th>
<th>1. ORGANIZATION</th>
<th>2. NDA NUMBER</th>
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<tbody>
<tr>
<td></td>
<td>DMEDP II, HFD-510</td>
<td>19-766</td>
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<thead>
<tr>
<th>3. NAME AND ADDRESS OF APPLICANT</th>
<th>4. SUPPLEMENT NUMBER, DATE</th>
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<tbody>
<tr>
<td>Merck Research Labs.</td>
<td>SCS-025</td>
</tr>
<tr>
<td>P.O. Box 4, BLA-20</td>
<td>7-25-97</td>
</tr>
<tr>
<td>West Point, PA 19486</td>
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<tr>
<th>5. PROPRIETARY NAME</th>
<th>6. NAME OF THE DRUG</th>
<th>7. AMENDMENTS, REPORT, DATE</th>
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<tbody>
<tr>
<td>Zocor Tablets</td>
<td>Simvastatin</td>
<td></td>
</tr>
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</table>

8. SUPPLEMENT PROVIDES FOR

The addition of a test and specification for the ____________________________________________________________________________________ in the simvastatin drug substance.

<table>
<thead>
<tr>
<th>9. PHARMACOLOGICAL CATEGORY</th>
<th>10. HOW DISPENSED</th>
<th>11. RELATED IND, NDA, DMF</th>
</tr>
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<tbody>
<tr>
<td>Antihypercholesteremic</td>
<td>RX</td>
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<table>
<thead>
<tr>
<th>12. DOSAGE FORM</th>
<th>13. POTENCY</th>
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</thead>
<tbody>
<tr>
<td>Tablets</td>
<td>10, 20, 40 mg</td>
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</tbody>
</table>

14. CHEMICAL NAME AND STRUCTURE

See Chemistry Review #1

15. COMMENTS

The sponsor intends to add a test and specification for the ____________________________________________________________________________________ for the drug substance simvastatin (structures provided p. 4), with a limit of ____________________________________________________________________________________ by peak area on the HPLC chromatogram. The sponsor claims that the impurity has probably always been present, but advances in analytical techniques have made it possible to accurately detect and quantify this impurity. The impurity occurs due to the ____________________________________________________________________________________.

Therefore, the sponsor has also provided a test and specification for ____________________________________________________________________________________ in the ____________________________________________________________________________________ sheet for this substance. Batch analysis has provided evidence that ____________________________________________________________________________________, has been present at a level of about ____________________________________________________________________________________, of lovatatin for the past 4 years, consistently. A limit of ____________________________________________________________________________________, has been set for ____________________________________________________________________________________, in the drug substance is identical to that for Assay of the drug substance, except that the detection is done at ____________________________________________________________________________________, and the ____________________________________________________________________________________, is well separated from simvastatin by this method. Lastly, data from bulk drug substance lots produced during 1992-1997 were provided, and the largest amount of the impurity recorded has been ____________________________________________________________________________________.

16. CONCLUSION AND RECOMMENDATION

The sponsor has provided adequate justification for the proposed test and specification for ____________________________________________________________________________________, in the bulk drug substance. The method of analysis for this impurity is essentially identical to that approved for assay of the drug substance, however, this method will be validated by FDA labs. Issue an approval letter.

<table>
<thead>
<tr>
<th>17. NAME</th>
<th>18. REVIEWERS SIGNATURE</th>
<th>19. DATE COMPLETED</th>
</tr>
</thead>
<tbody>
<tr>
<td>WILLIAM K. BERLIN</td>
<td></td>
<td>10-23-97</td>
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DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-766/S025

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
NDA 19-766/S-025

MERCK RESEARCH LABORATORIES, INC.
Sumneytown Pike
West Point, PA 19486

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

Dear Dr. R. E. Silverman:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ZOCOR (Simvastatin) Oral Tablets

NDA Number: 19-766

Supplement Number: S-025

Date of Supplement: July 25, 1997

Date of Receipt: July 29, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 27, 1997, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
cc:
Original NDA 19-766/S-025
HFD-510/Div. Files
HFD-510/CSO/M. Simoneau

filename:

SUPPLEMENT ACKNOWLEDGEMENT
July 25, 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:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

NDA 19-766: ZOCOR™ (Simvastatin)

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70(c), we submit, for your approval, a supplement to NDA 19-766.

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in Item 3 of the approved New Drug Application for ZOCOR™.

The attached supplemental application provides for the addition of a test method and specification for a _______ in simvastatin drug substance. _______ is not a new _______ in simvastatin; however, it has only currently been observed due to recent studies using the advanced technology of mass spectroscopy.

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

As required by Section 306(k)(l) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(l)], 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 Supplemental New Drug Application to be a confidential matter, and request the Food and Drug Administration not to 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 supplemental application 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 yours,

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

Attachments

Certified No. P. 963 213 144

Desk Copy: Philadelphia District Office, FDA
U.S. Custom House, Room 900
2nd & Chestnut Streets
Philadelphia, PA 19106-2973