Approval Package for:

APPLICATION NUMBER:
NDA 20-702/S013

Trade Name: Lipitor

Generic Name: Atorvastatin calcium

Sponsor: Parke-Davis Research and Development

Approval Date: June 25, 1998
# Contents

Reviews / Information Included in this NDA Review.

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APPLICATION NUMBER:
NDA 20-702/S013

APPROVAL LETTER
NDA 20-702/S-013

Parke-Davis
Attention: Philip G. Simonson, Ph.D.
Senior Manager, CMC, Worldwide Reg. Affairs
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, Michigan 48106-1047

Dear Dr. Simonson:


The user fee goal date for this application is October 2, 1998.

This supplemental new drug application provides for the addition an procedure for atorvastatin calcium drug substance.

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

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

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

Sincerely,

Stephen K. Moore 6/25/98

Stephen K. Moore, Ph.D.
Chemistry Team Leader I for
Division of Metabolic and Endocrine Drug Products (HFD-510)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
cc:
Archival NDA 20-702
HFD-510/Div. Files
HFD-510/M. Simoneau
HFD-95/DDMS
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: Mas/June 22, 1998
final:Mas6.25.98
filename: 70201.13

APPROVAL (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-702/S013

CHEMISTRY REVIEW(S)
# CHEMIST'S REVIEW

<table>
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<th>1. ORGANIZATION</th>
<th>CDER/HFD-510 Division of Metabolism and Endocrine Drug Products</th>
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<tbody>
<tr>
<td>2. NDA #</td>
<td>20-702 Approved: 17-DEC-1996</td>
</tr>
<tr>
<td>3. NAME AND ADDRESS OF APPLICANT</td>
<td>Parke-Davis Pharmaceutical Research</td>
</tr>
<tr>
<td>Division of Warner-Lambert Company</td>
<td></td>
</tr>
<tr>
<td>2800 Plymouth Road</td>
<td></td>
</tr>
<tr>
<td>P.O. Box 1047</td>
<td></td>
</tr>
<tr>
<td>Ann Arbor, MI 48106-1047 (313) 966-5000</td>
<td></td>
</tr>
<tr>
<td>5. Name of the Drug</td>
<td>Lipitor Tablets</td>
</tr>
<tr>
<td>6. NONPROPRIETARY NAME</td>
<td>Atorvastatin Calcium</td>
</tr>
<tr>
<td>7. SUPPLEMENT PROVIDES</td>
<td>procedure for Atorvastatin Calcium drug substance.</td>
</tr>
<tr>
<td>8. AMENDMENT</td>
<td>--</td>
</tr>
<tr>
<td>9. PHARMACOLOGICAL CATEGORY</td>
<td>Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.</td>
</tr>
<tr>
<td>10. HOW DISPENSED</td>
<td>N. A.</td>
</tr>
<tr>
<td>11. RELATED</td>
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</tr>
<tr>
<td>12. DOSAGE FORM</td>
<td>Tablet</td>
</tr>
<tr>
<td>13. POTENCY</td>
<td>10, 20 and 40 mg</td>
</tr>
<tr>
<td>14. CHEMICAL NAME AND STRUCTURE</td>
<td>Atorvastatin Calcium</td>
</tr>
<tr>
<td>(C&lt;sub&gt;33&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;F&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;5&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Ca</td>
<td></td>
</tr>
<tr>
<td>CAS 134523-03-8</td>
<td></td>
</tr>
<tr>
<td>CAS 134523-00-5 (atorvastatin)</td>
<td></td>
</tr>
<tr>
<td>FW 2 x 557.7 + 40.0 = 1155.38</td>
<td></td>
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<tr>
<td>FW calcium salt trihydrate (C&lt;sub&gt;33&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;F&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;5&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Ca.3H&lt;sub&gt;2&lt;/sub&gt;O = 1209.42</td>
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<tr>
<td>FW free acid C&lt;sub&gt;33&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;F&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;5&lt;/sub&gt; = 558.66</td>
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</tr>
<tr>
<td>1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-,calcium salt (2:1). [R, R'].</td>
<td></td>
</tr>
<tr>
<td>15. COMMENTS</td>
<td>The supplement (SCS-013, ref. # 13) provides for an additional procedure for Atorvastatin Calcium drug substance. In the approved NDA procedure, Atorvastatin that does not meet specifications is Atorvastatin. The new procedure, adequately described in attachment 1, does not lots of Atorvastatin calcium manufactured in Holland, Michigan, and manufactured in Warner-Lambert Export, Cork, Ireland) reworked using the procedure are provided in attachment 2. All lots meet the approved NDA analytical specifications.</td>
</tr>
<tr>
<td>16. CONCLUSIONS AND RECOMMENDATIONS</td>
<td>Adequate information has been provided to support the new procedure for the manufacture of Atorvastatin Calcium drug substance. Issue Approval Letter.</td>
</tr>
<tr>
<td>17. REVIEWER NAME (AND SIGNATURE)</td>
<td>Xavier Ysenn, PhD</td>
</tr>
<tr>
<td>DATE COMPLETED</td>
<td>12-MAY-1998</td>
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<td>R/D INITIATED BY</td>
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**filename:** nda/20702s13.doc

**DISTRIBUTION:** Original: NDA 20-702 cc: HFD-510 Division File / CSO / MooreS/ YsennX

**AP**

**Stephen K. Moore**

**5/20/98**
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-702/S013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
April 1, 1998

NDA 20-702
Ref. No. 62
Lipitor® (atorvastatin calcium) Tablets

Re: Supplement -

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Reference is made to NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets. The NDA is being supplemented to add an ______ procedure for atorvastatin drug substance.

The new ______ procedure is intended for ______ atorvastatin calcium ______ The procedure is described, for a suitable scale of operation, in Attachment 1.

In the approved NDA procedure, atorvastatin which does not meet specifications is approved synthesis to produce atorvastatin. The new procedure does not ______ atorvastatin calcium.

The suitability of this new rework procedure has been demonstrated on production scale. The analytical results for ______ lots of atorvastatin calcium ______ manufactured in Holland and ______ manufactured in Warner-Lambert Export) reworked using the new procedure are provided in Attachment 2. All lots meet the approved NDA analytical specifications.
Should you have any questions or require additional information, please contact me at 734/622-5781 or FAX 734/622-7890.

Sincerely,

Philip G. Simonson, Ph.D.
Senior Manager
Chemistry, Manufacturing and Control
Worldwide Regulatory Affairs
PARKE-DAVIS RESEARCH AND DEVELOPMENT
WARNER-LAMBERT COMPANY
2800 Plymouth Road
Ann Arbor, MI 48105

Attention: Philip G. Simonson, Ph.D.
Senior Manager, CMC Worldwide Regulatory Affairs

Dear Dr. Simonson:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: LIPITOR (atorvastatin calcium) Tablets
NDA Number: 20-702
Supplement Number: S-013
Date of Supplement: April 01, 1998
Date of Receipt: April 02, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 01, 1998, 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 20-702/S-013
  HFD-510/Div. Files
  HFD-510/CSO/M. Simoneau

filename: C:\DATA\WPFILES\20702ACK

SUPPLEMENT ACKNOWLEDGEMENT
1. APPLICANTS NAME AND ADDRESS
Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Rd.
Ann Arbor, MI 48105

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT
William Rosen
Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

3. TELEPHONE NUMBER (INCLUDE AREA CODE) (734)622-5168

4. PRODUCT NAME
Lipitor® Tablets

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?
☐ YES ☒ NO

6. USER FEE I.D. NUMBER

7. LICENSE NUMBER

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2)
(See reverse before checking box.)

☐ A CRUDE ALLERGIC EXTRACT PRODUCT

☐ OTHER: Orphan Drug - See attached.

☐ FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?
☐ YES (See reverse if answered YES) ☐ NO

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?
☐ YES (See reverse if answered YES) ☐ NO

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE
Sean Brennan

TITLE
Senior Manager
Worldwide
Regulatory Affairs

DATE
April 1, 1998