CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER: NDA 20-702/S010

Trade Name: Lipitor

Generic Name: Atorvastatin calcium

Sponsor: Parke-Davis Research and Development

Approval Date: April 29, 1998
**CONTENTS**

**Reviews / Information Included in this NDA Review.**

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<td>X</td>
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**APPLICATION NUMBER:**

NDA 20-702/S-010

**CENTER FOR DRUG EVALUATION AND RESEARCH**
APPLICATION NUMBER:
NDA 20-702/S010

APPROVAL LETTER
Dear Mr. Simonson:


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

The supplemental application provides for the use of Warner-Lambert Cork, Ltd., Ringaskiddy, Ireland as an additional manufacturing site for Lipitor and 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, please contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely yours,

Stephen K. Moore, Ph.D.
Chemistry Team Leader I, DNDCII
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
cc:
Original NDA 20-702
HFD-510/Div. Files
HFD-510/CSO/M. Simoneau
HFD-510/X.Ysern/S.Moore/E.Galliers
HFD-820/ONDC Division Director
HFD-92/DDM-DIAB
DISTRICT OFFICE

Drafted by: Mas/April 28, 1998/20.702.10
Initialed by: X.Ysern4.28.98/S.Moore4.28.98/E.Galliers4.28.98
final: Mas4.29.98

APPROVAL (AP)

FOI: Please redact the phrase, ______ from the above.
**CHEMIST'S REVIEW**

<table>
<thead>
<tr>
<th>1. ORGANIZATION</th>
<th>CDER/HFD-510</th>
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</thead>
<tbody>
<tr>
<td>Division of Metabolism and Endocrine Drug Products</td>
<td>2. NDA # 20-702</td>
</tr>
<tr>
<td></td>
<td>Approved: 17-DEC-1996</td>
</tr>
<tr>
<td>3. NAME AND ADDRESS OF APPLICANT</td>
<td>4. SUPPLEMENT SCM-010</td>
</tr>
<tr>
<td>Division of Warner-Lambert Company</td>
<td></td>
</tr>
<tr>
<td>2800 Plymouth Road</td>
<td>5. Name of the Drug Lipitor Tablets</td>
</tr>
<tr>
<td>P.O. Box 1047</td>
<td></td>
</tr>
<tr>
<td>Ann Arbor, MI 48106-1047</td>
<td>6. Nonproprietary Name Atorvastatin Calcium</td>
</tr>
<tr>
<td>(313) 966-5000</td>
<td></td>
</tr>
<tr>
<td>7. SUPPLEMENT PROVIDES for the use of Warner-Lambert Cork, Ltd., Ringaskiddy, Ireland, as an additional manufacturing site for and Atorvastatin Calcium drug substance.</td>
<td>8. AMENDMENT --</td>
</tr>
<tr>
<td>9. PHARMACOLOGICAL CATEGORY Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.</td>
<td>10. HOW DISPENSED</td>
</tr>
<tr>
<td>11. RELATED</td>
<td>-N, A.-</td>
</tr>
<tr>
<td>12. DOSAGE FORM Tablet</td>
<td>13. POTENCY 10, 20 and 40 mg</td>
</tr>
<tr>
<td>14. CHEMICAL NAME AND STRUCTURE</td>
<td>Atorvastatin Calcium</td>
</tr>
<tr>
<td>(C₃₃H₄₃FN₂O₇)₂Ca</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>
</tr>
<tr>
<td>FW calcium salt trihydrate (C₃₃H₄₃FN₂O₇)₂Ca.3H₂O = 1209.42</td>
<td></td>
</tr>
<tr>
<td>FW free acid C₃₃H₃₅FN₂O₅ = 588.66</td>
<td></td>
</tr>
<tr>
<td>1H-Pyrrole-1-heptanoic acid, 2-(4-flourophenyl)-β,δ-dihydroxy-5-(1-methyllethyl)-3-phenyl-4-[(phenylaminocarbonyl]-calcium salt 2:1, [R-(R*,R*)]-</td>
<td></td>
</tr>
<tr>
<td>15. COMMENTS</td>
<td>The method of synthesis and the manufacturing process to be used at the Warner-Lambert Cork facility are unchanged from the approved NDA. Batches of material and Atorvastatin Calcium) manufactured at the Cork facility have the same characteristics as that manufactured at the approved facilities. Acceptable cGMP for the Sponsor facility located in Rinaskiddy, County Cork (Ireland) was given by the District Office on February 5, 1998.</td>
</tr>
<tr>
<td>16. CONCLUSIONS AND RECOMMENDATIONS</td>
<td>Adequate information has been provided to support the use of the Warner-Lambert Export, Ltd., facility located in Cork (Ireland) for the manufacture of for and Atorvastatin Calcium drug substance. <strong>Issue Approval Letter.</strong></td>
</tr>
<tr>
<td>17. REVIEWER NAME (AND SIGNATURE)</td>
<td>Xavier Ysenn, PhD</td>
</tr>
<tr>
<td>DATE COMPLETED</td>
<td>20/APR/1998</td>
</tr>
<tr>
<td>R/D INITIATED BY</td>
<td></td>
</tr>
<tr>
<td>DISTRIBUTION: Original: NDA 20-702 cc: HFD-510 Division File / CSO / MooreS/ YsennX</td>
<td></td>
</tr>
</tbody>
</table>

**AP**

Stephen K. Moore
4/22/98
3__ Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

______ § 552(b)(4) Draft Labeling

______ § 552(b)(5) Deliberative Process
CDER Establishment Evaluation Report
for March 02, 1998

Application: NDA 20702/010
Applicant: PARKE DAVIS
2800 PLYMOUTH RD
ANN ARBOR, MI 481061047

Priority: 1P
Org Code: 510
Brand Name: LIPITOR (ATORVASTATIN CALCIUM) 10/20/40MG

Established Name:
Generic Name: ATORVASTATIN CALCIUM
Dosage Form: TAB (TABLET)
Strength: 10, 20 AND 40 MG

FDA Contacts: X. YSERN (HFD-510) 301-827-6430, Review Chemist

Overall Recommendation:
ACCEPTABLE on 05-FEB-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9612161
WARNER LAMBERT EXPORT LTD
LOUGH Beg
RINGASKIDDY, COUNTY CORK, EI

DMF No:
AADA No:

Profile: CSN OAI Status: NONE Responsibilities: DRUG SUBSTANCE MANUFACTURER
Last Milestone: OC RECOMMENDATION
Milestone Date 05-FEB-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-702/S010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
January 28, 1998

NDA 20-702
Ref. No. 59
Lipitor® (atorvastatin calcium) Tablets

Re: Special Supplement
Changes Being Effected:
Additional Drug Substance
 Manufacturing Facility –
Warner-Lambert Cork, Ltd.

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

Dear Dr. Sobel:

Reference is made to NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets, and to a telephone conversation on September 16, 1997, between Dr. S. Brennan and myself of Parke-Davis and Dr. X. Ysenn of your Division. The purpose of this supplement is to provide for the use of Warner-Lambert Cork, Ltd., Ireland as an additional manufacturing site for and atorvastatin calcium drug substance. This change will be implemented in January 1998.

Our currently approved manufacturing facilities are Holland, Michigan, and Warner-Lambert Export, Ltd. (formerly Warner-Lambert Plaistow Manufacturing Partnership). The method of synthesis and the manufacturing process to be used at the Warner-Lambert Cork facility are unchanged from the approved NDA. The address of the Warner-Lambert Cork facility is:

Warner-Lambert Cork, Ltd. (formerly Hickson Pharmachem, Ltd.)
Loughbeg, Ringaskiddy
County Cork
IRELAND
Phone: 353-21-378870
FAX: 353-21-378880
Solomon Sobel, M.D.
NDA 20-702
January 28, 1998
Page 2

In our discussions with Dr. Ysern, the requirements for the addition of ——— and atorvastatin calcium manufacturing at Warner-Lambert Cork were agreed upon. Pursuant to these agreements, the following are provided in the attachment to support the addition of Warner-Lambert Cork as a manufacturing site for ——— and atorvastatin calcium:

- Description of manufacturing process for atorvastatin calcium drug substance at Warner-Lambert Cork
- Comparison of the processes at Warner-Lambert Cork with the approved process
- Batch analysis summary for / lots of ——— manufactured at Warner-Lambert Cork and used to prepare validation lots of atorvastatin calcium
- Batch analysis summary for / lots of atorvastatin calcium manufactured at Warner-Lambert Cork
- Comparison of Warner-Lambert Cork analytical results to historical results of batches manufactured at the approved facilities
- Specifications and analytical Methods for starting materials and intermediates used at Warner-Lambert Cork

This facility was inspected by the FDA on March 27, 28, and 29, 1997 and no FDA form 483 was issued.

Should you have any questions regarding this submission, please contact me at 313/996-5781 or FAX 313/996-7890 or Dr. Sean Brennan at 313/996-7596.

Sincerely,

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

Desk Copy: Ms. Regina Brown, North Brunswick FDA District Office
Dr. Xavier Ysern, Division of Metabolism and Endocrine Drug Products
Parke-Davis Research and Development
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

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

Dear Dr. P. G. Simonson:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: LIPITOR (atorvastatin) Tablets
NDA Number: 20-702
Supplement Number: S-010
Date of Supplement: January 28, 1998
Date of Receipt: January 29, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 30, 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,

[Signature]

Ann 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-010
  HFD-510/Div. Files
  HFD-510/CSO/M. Simoneau

filename:

SUPPLEMENT ACKNOWLEDGEMENT
# USER FEE COVER SHEET

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any aspect of this collection of information, including suggestions for reducing this burden, to:

- Reports Clearance Officer, PhS
- Hubert Humphrey Building, Room 721-B
- 200 Independence Avenue, S.W.
- Attn: PRA

and to:

- Office of Management and Budget
- Paperwork Reduction Project (0910-0297)
- Washington, DC 20500

Please DO NOT RETURN this form to either of these addresses.

---

### 1. APPLICANTS NAME AND ADDRESS

Parke-Davis Research and Development  
Division of Warner-Lambert Company  
2800 Plymouth Rd.  
Ann Arbor, MI 48105

### 2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Mary E. Taylor, MPH  
Parke-Davis Research and Development  
Warner-Lambert Company  
2800 Plymouth Road  
Ann Arbor, MI 48105

### 3. TELEPHONE NUMBER (INCLUDE AREA CODE)

(313)996-5000

### 4. PRODUCT NAME

Lipitor® Tablets

### 5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?

- [ ] YES  
- [x] NO

**IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.**

### 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.

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<thead>
<tr>
<th>Option</th>
<th>Description</th>
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<td>A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/82</td>
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<tr>
<td>[ ]</td>
<td>AN INSULIN PRODUCT SUBMITTED UNDER 506</td>
</tr>
<tr>
<td>[ ]</td>
<td>FOR BIOLOGICAL PRODUCTS ONLY</td>
</tr>
<tr>
<td>[ ]</td>
<td>WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION</td>
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<td>[ ]</td>
<td>BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/82</td>
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<td>THE APPLICATION IS SUBMITTED UNDER 505(b)(2) (See reverse before checking box.)</td>
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<td>OTHER: ORPHAN DRUG - SEE ATTACHED.</td>
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<tr>
<td>[ ]</td>
<td>A CRUDE ALLERGIC EXTRACT PRODUCT</td>
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<td>[ ]</td>
<td>AN &quot;IN VITRO&quot; DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT</td>
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### 9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?

- [ ] YES (See reverse if answered YES)  
- [x] NO

### 9. b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

- [ ] YES (See reverse if answered YES)  
- [x] NO

---

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

**SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE**:  
Leslie Bloom

**TITLE**:  
Director Worldwide Regulatory Affairs

**DATE**:  
January 28, 1998