CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-702/S009

Trade Name: Lipitor

Generic Name: Atorvastatin calcium

Sponsor: Parke-Davis Research and Development

Approval Date: March 23, 1998
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-702/S-009

CONTENTS

Reviews / Information Included in this NDA Review.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-702/S009

APPROVAL LETTER
Dear Mr. Brennan:

Please refer to your supplemental new drug application dated December 4, 1997, received December 5, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.7(c) for Lipitor (atorvastatin calcium) tablets.

The User Fee goal date for this application is June 5, 1998. Your submission stated that the change was to be implemented in December 1997.

The supplemental application provides for a modification of the manufacturing process for the __________ in the Freiburg, Germany facility.

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,

[Signature]

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
cc:
Original NDA 20-702
HFD-510/Div. Files
HFD-510/CSO/M. Simoneau
HFD-510/X.Ysenn/S.Moore/C.Jones/H.Ahn /E.Galliers
HFD-820/ONDC Division Director
HFD-92/DDM-DIAB
DISTRICT OFFICE

Drafted by: Mas/March 13, 1998/207029
Initialed
final: Mas3.23.98

APPROVAL (AP)

FOI: Please redact the phrase “———” from the above.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-702/S009

CHEMISTRY REVIEW(S)
**CHEMIST'S REVIEW**

1. **ORGANIZATION**  CDER/HFD-510  
Division of Metabolism and Endocrine Drug Products

2. **NDA #** 20-702  
Approved: 17-DEC-1996

3. **NAME AND ADDRESS OF APPLICANT**  
Parke-Davis Pharmaceutical Research Division  
Warner-Lambert Company  
2800 Plymouth Road  
P.O. Box 1047  
Ann Arbor, MI 48106-1047  
(313) 966-5000

4. **SUPPLEMENT**  SCM-009  
Doc 04-DEC-1997  Rec 05-DEC-1997

5. **Name of the Drug**  Lipitor Tablets

6. **Nonproprietary Name**  Atorvastatin Calcium

7. **SUPPLEMENT PROVIDES**  for a modification of the manufacturing process for the size of the drug product.

8. **AMENDMENT**  --

9. **PHARMACOLOGICAL CATEGORY**  Lipid Modifier.  
HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.

10. **HOW DISPENSED**  R  
11. **RELATED**  -N. A.-

12. **DOSAGE FORM**  Tablet  
13. **POTENCY**  10, 20 and 40 mg

**14. CHEMICAL NAME AND STRUCTURE**  
Atorvastatin  
(C_{26}H_{34}FN_{2}O_{5})_2Ca  
FW anhydrous calcium salt 2 x 557.7 + 40.0 = 1155.38  
FW calcium salt trihydrate (C_{26}H_{34}FN_{2}O_{5})_2Ca·3H_{2}O = 1209.42  
FW free acid C_{26}H_{34}FN_{2}O_{5} = 558.66  

\[ R-\{R^*,R^*\}]-2-(4-fluorophenyl)-5,5-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) \]

15. **COMMENTS**  
The proposed change takes place in the manufacture. After the manufacturing steps are:  
Manufacture's in-process controls remain the same from the original NDA. In the currently approved process the proposed is the final blend is prepared as it is by the currently approved process. The applicant provides data to show that there are no significant differences between tablets manufactured using the approved size and the proposed. Acceptable cGMP for the Sponsor facility located in Freiburg (Germany) was given by the District Office on January 15, 1998.

16. **CONCLUSIONS AND RECOMMENDATIONS**  
Adequate information has been provided to support the proposed modification of the manufacture of the drug product. Issue Approval Letter.

17. **REVIEWER NAME (AND SIGNATURE)**  Xavier Ysem, PhD  
**DATE COMPLETED**  30-JAN-1998

**R/D INITIATED BY**  
filename: 20702s09.nda

**DISTRIBUTION:**  
Original: NDA 20-702  cc: HFD-510 Division File  CSO  Reviewer
3 Page(s) Withheld

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

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-20-702509
CDER Establishment Evaluation Report
for January 22, 1998

Application: NDA 20702009
Stamp: 05-DEC-1997 Regulatory Date: 05-JUN-1998
Applicant: PARKE DAVIS
2800 PLYMOUTH RD
ANN ARBOR, MI 481061047

Priority: 1P Org Code: 510
Action Goal: DISTRICT GOAL
District Goal: 01-MAR-1998
Brand Name: LIPITOR (ATORVASTATIN CALCIUM) 10/20/40 MG

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 15-JAN-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9611594
DMF No:
GODECKE AG
MOOSWALDALLE 1
FREIBURG, GM
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-JAN-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-702/S009

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)
NDA: 20-702

SUBMISSION DATE: December 4, 1997

BRAND NAME: Lipitor™

GENERIC NAME: Atorvastatin calcium tablets

REVIEWER: Carolyn D. Jones, Ph.D.

SPONSOR: Parke-Davis Pharmaceutical Research
Ann Arbor, Michigan

Type of Submission: Special Supplement-Changes Being Effect
Manufacturing Process Change

SYNOPSIS:

The purpose of the supplement is to modify the manufacturing process for the ___________ in the Freiburg, Germany facility. The change was implemented in December, 1997. In the currently approved manufacturing process the ___________ is performed ___________. In the proposed method the ___________ s are prepared from ___________.

The sponsor included comparative dissolution profiles in water (the approved medium at the time of this submission) for ___________ lots of Lipitor™ tablets manufactured by the proposed process and the Freiburg NDA stability/process validation lots. No differences were observed in dissolution of tablets manufactured by the proposed method and existing methods.

RECOMMENDATION:

No action is required by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII). The submission was provided to this group for informational purposes only.

Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II

2/26/98

RD/FT initialed by Hae-Young Ahn, Ph.D. Team Leader 2/28/98

cc: NDA 20-702, HFD-510(Ysern, Simoneau), HFD-870(Jones, Ahn, M. Chen), CDR(Murphy)

CODE: NL
APPLICATION NUMBER:
NDA 20-702/S009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
December 4, 1997

NDA 20-702
Ref. No. 54
Lipitor® (atorvastatin calcium) Tablets

Re: Special Supplement -
Changes Being Effected:
Manufacturing Process Change

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 our approved NDA 20-702 for Lipitor® (atorvastatin calcium) 10, 20, and 40 mg tablets. Reference is also made to a telephone conversation between myself and Dr. Philip Simonson of Parke-Davis and Dr. Xavier Ysem of your Division on June 18, 1997. The purpose of this supplement is to modify the manufacturing process for the ________ in the Freiburg, Germany facility. This change will be implemented in December 1997.

In the currently approved manufacturing process for the ________, the ________ is performed in ______ according to the manufacturing directions for the ________. This involves _______. The ________ are then ________.

In the proposed ________, ________ is __________. The ________ is ________.

The final blend is prepared as it is by the currently approved ________. 26/98
In our conversation with Dr. Ysern on June 18, the requirements for this process change were discussed. Pursuant to those discussions, the following are provided in Attachment 1 to support the proposed process modifications:

- A description of the proposed manufacturing process and a comparison to the approved process.
- Representative Master Batch Records for the proposed process.
- Specifications and Test Methods for Lipitor tablets.
- Batch analysis summary for lots of Lipitor tablets manufactured in Freiburg, Germany by the proposed process.
- Comparative dissolution profiles in the approved medium for lots of Lipitor tablets manufactured by the proposed process and the Freiburg NDA stability/process validation lots.
- A study report containing dissolution profiles of all lots used in bioequivalence studies (reproduced from the original NDA).

The data provided in Attachment 1 demonstrate that Lipitor tablets manufactured by the proposed process are equivalent to those manufactured by the currently approved manufacturing process. Pursuant to 21 CFR 314.440(a)(4), a copy of this submission is also provided to the FDA District Office in North Brunswick, New Jersey.

If you have any questions or need additional information, please contact me at 313/996-7596, Phil Simonson at 313/996-5781, or FAX 313/996-7890.

Sincerely,

Sean Brennan

SB\ps\rm
\tn\nda\20-7021\20497-54

Attachments

Copy: Dr. X. Ysern
Ms. R. Brown, North Brunswick District Office
NDA 20-702/S-009

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

Attention: Sean Brennan, R. Ph., Senior Director, Worldwide Regulatory Affairs

Dear Dr. S. Brennan:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: LIPITOR® (atorvastatin) TABLETS

NDA Number: 20-702

Supplement Number: S-009

Date of Supplement: December 4, 1997

Date of Receipt: December 5, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on January 3, 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]

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-009
  HFD-510/Div. Files
  HFD-510/CSO/M. Simoneau

filename:

SUPPLEMENT ACKNOWLEDGEMENT
**USER FEE COVER SHEET**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**PUBLIC HEALTH SERVICE**  
**FOOD AND DRUG ADMINISTRATION**

**Form Approved: OMB No. 0910-0297**  
**Expiration Date: November 30, 1996**

**See Instructions on Reverse Before Completing This Form**

<table>
<thead>
<tr>
<th>1. APPLICANTS NAME AND ADDRESS</th>
<th>2. USER FEE BILLING NAME, ADDRESS, AND CONTACT</th>
</tr>
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</table>
| Parke-Davis Research and Development  
Division of Warner-Lambert Company  
2800 Plymouth Rd.  
Ann Arbor, MI 48105 | Mary E. Taylor, MPH  
Parke-Davis Research and Development  
Warner-Lambert Company  
2800 Plymouth Road  
Ann Arbor, MI 48105 |

<table>
<thead>
<tr>
<th>3. TELEPHONE NUMBER (INCLUDE AREA CODE)</th>
<th>(313)996-5000</th>
</tr>
</thead>
</table>

<table>
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<tr>
<th>4. PRODUCT NAME</th>
<th>Lipitor® Tablets</th>
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**5 DOES THIS APPLICATION CONTAIN CLINICAL DATA?**  
☐ YES  ☒ NO

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

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<th>6. USER FEE I.D. NUMBER</th>
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**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 FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

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

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) (See reverse before checking box.)  
☐ A CRUDE ALLERGIC EXTRACT PRODUCT

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

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<th>9. b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?</th>
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<tr>
<td>☐ YES  (See reverse if answered YES)</td>
<td>☐ YES  (See reverse if answered YES)</td>
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**This completed form must be signed and accompany each new drug or biologic product, original or supplement.**

**SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE**  
Mary E. Taylor

**TITLE**  
Director  
Worldwide  
Regulatory Affairs

**DATE**  
December 4, 1997

**FORM FDA 3397 (12/93)**