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

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Reviews / Information Included in this NDA Review.

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Approvable Letter	
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Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-702/S009

APPROVAL LETTER

NDA 20-702/S-009

MAR 23 1998

Parke-Davis Pharmaceutical Research
Attention: Sean Brennan, R.Ph.
Division of Warner-Lambert Company
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

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,

Stephen K. Moore 3/23/98

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.Ysern/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
by:X.Ysern3.13.98/S.Moore3.13.98/C.Jones3.13.98/H.Ahn3.16.98/E.Galliers3.20.98
final: Mas3.23.98

APPROVAL (AP

FOI: Please redact the phrase " [redacted] **from the above.**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-702/S009

CHEMISTRY REVIEW(S)

FEB - 9 1998

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
℞

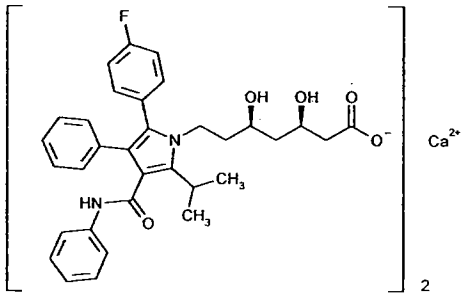
11. RELATED
-N. A.-

12. DOSAGE FORM Tablet

13. POTENCY 10, 20 and 40 mg

14. CHEMICAL NAME AND STRUCTURE
Atorvastatin
$(C_{33}H_{34}FN_2O_5)_2Ca$
FW anhydrous calcium salt 2 x 557.7 + 40.0 = 1155.38
FW calcium salt trihydrate $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ = 1209.42
FW free acid $C_{33}H_{34}FN_2O_5$ = 558.66

[*R*-(*R**,*R**)]-2-(4-flourophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrole-1-heptanoic acid calcium salt (2:1)



15. COMMENTS The proposed change takes place in the ——— of the drug product manufacture. After ——— the manufacturing steps are: ——— Manufacture's in-process controls remain the same from the original NDA. In the currently approved ——— according to the manufacture for the ——— In the proposed , the ——— are prepared from ——— The ——— and 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 Ysern
Xavier Ysern, 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

Stephen K. Moore
2/9/98

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- 20-702
5009

CDER Establishment Evaluation Report for January 22, 1998

Application: NDA 20702/009
Stamp: 05-DEC-1997 Regulatory Due: 05-JUN-1998
Applicant: PARKE DAVIS
2800 PLYMOUTH RD
ANN ARBOR, MI 481061047

Priority: 1P Org Code: 510
Action Goal: District Goal: 31-MAR-1998
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 15-JAN-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9611504
GODECKE AG
MOOSWALDALLE 1
FREIBURG, , GM

DMF No:
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)

Clinical Pharmacology & Biopharmaceutics Review

FEB 28 1998

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 Effected Manufacturing Process Change**

SYNOPSIS:

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

The sponsor included comparative dissolution profiles in water (the approved medium at the time of this submission) for [redacted] 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 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

2/26/98
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-702/S009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Pharmaceutical Research
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: 313-996-7596
Facsimile: 313-996-7890

NDA SUPPLEMENT ORIGINAL

NDA NO. 20702 REF. NO. 009

NDA SUPPL FOR SCM

PARKE-DAVIS
People Who Care

Sean Brennan, Ph.D.
Senior Director
Worldwide Regulatory Affairs

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 Ysern of your Division on June 18, 1997. The purpose of this supplement is to modify the manufacturing process for the [redacted] in the Freiburg, Germany facility. This change will be implemented in December 1997.

In the currently approved manufacturing process for the [redacted], the [redacted] is performed in [redacted] according to the manufacturing directions for the [redacted]. This involves [redacted] The [redacted] are then [redacted]

In the proposed [redacted] The [redacted] is [redacted] The [redacted] the final blend is prepared as it is by the currently approved [redacted]

CDS 2/26/98

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

Sean Brennan

SB\ps\rm
t:\nda\20-702\120497-54

Attachments

Copy : Dr. X. Ysern
Ms. R. Brown, North Brunswick District Office

REVIEWS COMPLETED
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
MDo 3/23/98 AP ltr
CSO INITIALS DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-702/S-009

DEC 12 1997

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,

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

12-10-97

filename:

SUPPLEMENT ACKNOWLEDGEMENT

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

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

USER FEE COVER SHEET

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, gathering and ...aining the data needed, 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 2050

Please DO NOT RETURN this form to either of these addresses

See Instructions on Reverse Before Completing This Form

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 ☒ 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.

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

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

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGIC EXTRACT PRODUCT

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

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

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	TITLE	DATE
Mary E Taylor	Director Worldwide Regulatory Affairs	December 4, 1997

FORM FDA 3397 (12/93)