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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-702/S-010

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Reviews / Information Included in this NDA Review.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-702/S010

APPROVAL LETTER

NDA 20-702/S-010

ORIGINAL

APR 29 1998

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Philip G.Simonson, Ph.D.
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Mr. Simonson:

Please refer to your supplemental new drug application dated January 28, 1998, received January 29, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lipitor (atorvastatin calcium) Tablets.

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 [redacted] 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 4/29/98

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, ' [redacted] **from the above.**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-702/S010

CHEMISTRY REVIEW(S)

APR 2 2 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 of Warner-Lambert Company
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047 (313) 966-5000

4. SUPPLEMENT SCM-010
Doc 28-JAN-1998 Rec 29-JAN-1998

5. Name of the Drug Lipitor Tablets

6. Nonproprietary Name
Atorvastatin Calcium

7. SUPPLEMENT PROVIDES for the use of Warner-Lambert Cork, Ltd., Ringaskiddy, Ireland, as an additional manufacturing site for [redacted] and Atorvastatin Calcium drug substance.

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

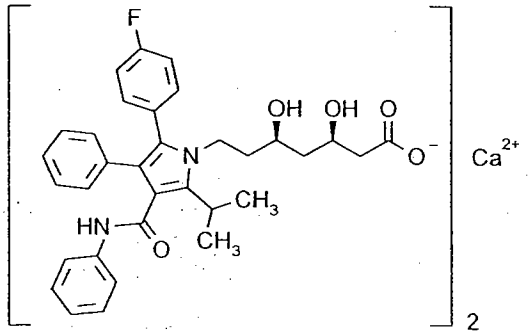
14. CHEMICAL NAME AND STRUCTURE

Atorvastatin Calcium

$(C_{33}H_{34}FN_2O_5)_2Ca$

CAS 134523-03-8
CAS 134523-00-5 (atorvastatin)

FW 2 x 557.7 + 40.0 = 1155.38
FW calcium salt trihydrate $(C_{33}H_{34}FN_2O_5)_2Ca.3H_2O$ = 1209.42
FW free acid $C_{33}H_{35}FN_2O_5$ = 558.66



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

15. COMMENTS 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 [redacted] 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.

16. CONCLUSIONS AND RECOMMENDATIONS 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 [redacted] and Atorvastatin Calcium drug substance. **Issue Approval Letter**.

17. REVIEWER NAME (AND SIGNATURE) **DATE COMPLETED** 20-APR-1998
Xavier Ysern, PhD Xavier Ysern

R/D INITIATED BY

filename: /nda/20702s10.doc

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

AP
Stephen K. Moore 4/22/98

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- 20-762
5010

CDER Establishment Evaluation Report
for March 02, 1998

Application: **NDA 20702/010**
Stamp: **29-JAN-1998** Regulatory Due: **29-JUL-1998**
Applicant: **PARKE DAVIS**
2800 PLYMOUTH RD
ANN ARBOR, MI 481061047

Priority: **1P** Org Code: **510**
Action Goal: District Goal: **24-MAY-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 05-FEB-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: **9612161**
WARNER LAMBERT EXPORT LTD
LOUGHBEG
RINGASKIDDY, COUNTY CORK, EI

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **05-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-702/S010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Pharmaceutical Research
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (313) 996-7000

ORIGINAL

NDA NO. 20702 REF. NO. 010

NDA SUPPL FOR SCM

PARKE-DAVIS

January 28, 1998

NDA SUPPLEMENT

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. Ysern 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 [redacted] 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

In our discussions with Dr. Ysern, the requirements for the addition of [redacted] 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 [redacted] 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 [redacted] 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.

REVIEWS COMPLETED

CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
Mao AP 4/29/98
CSO INITIALS DATE

Sincerely,

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

PS\rm t:\nda\20-702\012898-59

Attachments

Desk Copy: Ms. Regina Brown, North Brunswick FDA District Office
Dr. Xavier Ysern, Division of Metabolism and Endocrine Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES | Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-702/S-010

FEB 4 1998

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,

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

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

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

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

☐ Other: Orphan Drug - See attached.

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
Leslie Bloom for	Director Worldwide Regulatory Affairs	January 28, 1998

FORM FDA 3397 (12/93)