CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-702/S011

Trade Name: Lipitor

Generic Name: Atorvastatin calcium

Sponsor: Parke-Davis Research and Development

Approval Date: August 4, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-702/S-011

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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/S011

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-702/S-011

AUG 4 1998

Parke-Davis Research and Development
Attention: Sean Brennan, Ph.D.
Senior Director, Regulatory Affairs
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Dr. Brennan:

Please refer to your supplemental new drug application dated February 9, 1998, received February 10, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lipitor (atorvastatin calcium) Tablets, 10 mg.

We acknowledge receipt of your submission dated July 30, 1998.

The user fee goal date for this application is August 10, 1998.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c). You indicated that the implementation date for these changes for the Lipitor 10 mg tablet was February 1998.

This supplemental new drug application provides for the use of Parke-Davis Pharmaceutical, Limited (PDPL) facility at Vega Baja, Puerto Rico, as an additional site, including a [redacted] the manufacture of the 10 mg strength of Lipitor Tablets.

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 8/4/98

Stephen K. Moore, Ph.D.
Chemistry Team Leader I for
Division of Metabolism 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 (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: Mas/July 21, 1998
Initialed by:X.Ysern7.22&8.3.98/S.Moore7.22&8.3.98/H.Ahn7.24.98/E.Galliers7.26&8.3.98
final:Mas8.4.98
filename: 20702.11

APPROVAL (AP)

FOI: Please redact " [redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-702/S011

CHEMISTRY REVIEW(S)

AUG 3 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-011
Doc.09-FEB-1998 Rec.10-FEB-1998

5. Name of the Drug Lipitor Tablets

6. Nonproprietary Name
Atorvastatin Calcium

7. Supplement provides for the use of Parke-Davis Pharmaceutical, Limited (PDPL) at Vega Baja, Puerto Rico, as an additional site for the manufacture of Lipitor (Atorvastatin Calcium) 10 mg tablets

8. Amendment
Doc 30-JUL-1998 Rec 31-JUL-1998

9. Pharmacological Category Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.

10. How Dispensed

11. Related
-N. A.-

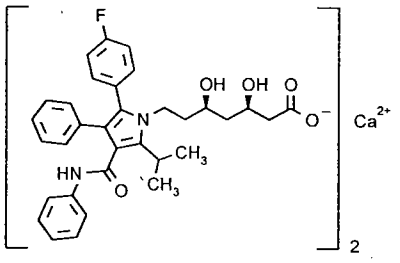
12. Dosage Form Tablet

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 This [SUPAC] supplement provides for the addition of a new facility, Parke-Davis Pharmaceuticals, Limited (PDPL), at Vega Baja (Puerto Rico), for the manufacture of the 10 mg strength Lipitor (Atorvastatin) Tablets. The original supplement also stated that information regarding would be incorporated into NDA 20720 Annual Reports. We informed Park-Davis that we will approve manufacture of the 10 mg tablets at the Vega Baja facility based on the information supplied in this supplement (see original review, 20720s11.doc).

16. Conclusions And Recommendations Adequate information has been provided to support the use of the Parke-Davis Pharmaceutical, Ltd., facility located in Vega Baja, Puerto Rico, for the manufacture of Lipitor (Atorvastatin Calcium) 10 mg tablets. **Issue Approval Letter.**

17. Reviewer Name (and signature) Xavier Ysern, PhD

Date Completed 03-AUG-1998

R/D Init.

filename: /nda/20702s11a.doc

DISTRIBUTION: Original: NDA 20-702 cc: HFD-510 Division File/ SMoore/ MSimoneau / XYsern

AP

Stephen K. Moore
8/3/98

_7___ Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-_____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-702/S011

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Pharmaceutical Research
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (734) 622-7596
Facsimile: (734) 622-7890

BC

ORIGINAL

PARKE-DAVIS

July 30, 1998

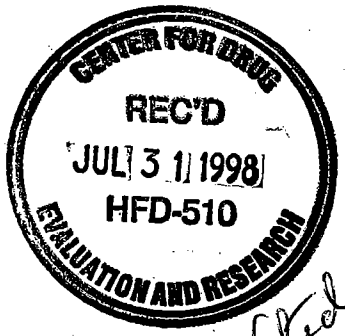
NDA SUPPL AMENDMT.

NDA 20-702/S-011
Ref. No. 75
Lipitor® (atorvastatin calcium) Tablets

Re: Amendment to Special Supplement
Changes Being Effected S-011:
Additional Drug Product
Manufacturing Facility –
Parke-Davis Pharmaceuticals, Ltd.

Sean Brennan, Ph.D.
Vice President
Worldwide Regulatory Affairs

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



Noted
X-Yuen
8/6/98
see cmc
review
nda 20702 S11
AP
X Yuen

Dear Dr. Sobel:

Reference is made to our approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets. Reference is also made to a Special Supplement – Changes Being Effected submitted on February 9, 1998, to provide for the use of Parke-Davis Pharmaceuticals, Limited (PDPL) as an additional manufacturing site for Lipitor 10, [redacted] tablets.

If you have any questions or need additional information, please contact me at 734/622-7596 or Phil Simonson at 734/622-5781, or FAX 734/622-7890.

Sincerely,

Leslie Bloom for

Sean Brennan

SB\rp\rm
t:\nda\20-702\073098-75

REVIEWS COMPLETED
CSO ACTION: AP
☑ LETTER ☐ N.A.I. ☐ MEMO
Mas 8-7-98
CSO INITIALS DATE

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. 60

NDA SUPPL FOR SCM

PARKE-DAVIS
People Who Care

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

February 9, 1998

NDA 20-702
Ref. No. 60
Lipitor® (atorvastatin calcium) Ta

Re: **Special Supplement**
Changes Being Effected:
Additional Drug Product
Manufacturing Facility –
Parke-Davis Pharmaceuticals, 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. X. Ysern of your Division, Dr. P. Simonson, and myself of Parke-Davis. The purpose of this supplement is to provide for the use of Parke-Davis Pharmaceuticals, Limited (PDPL) as an additional manufacturing site for Lipitor tablets. This change will be implemented for Lipitor 10 mg tablets in February 1998.

manufactured at the PDPL location.

Our currently approved manufacturing facilities are Freiburg, Germany (Goedecke A.G./Parke-Davis) and Lititz, Pennsylvania. The address of the PDPL facility is:

Parke-Davis Pharmaceuticals, Limited
Kilometer 1.9, Road 689
Vega Baja, Puerto Rico

1623619 SKumar 7/27/98

noted
ahn 6/18/98

27-JUL-1998 → talk to RD's Ross Poe

+ ltr. dated 30-JUL-19

In our discussions with Dr. Ysern, the requirements for the addition of atorvastatin calcium tablets manufacturing at PDPL were agreed upon. Pursuant to these agreements, the following are provided in the attachment to support the addition of PDPL as a manufacturing site for Lipitor 10 mg tablets:

- Comparison of the manufacturing process at Vega Baja to the approved process at Freiburg, Germany
- Representative Master Batch Records for the Vega Baja process
- Specifications and Analytical Methods for raw materials used at Vega Baja
- Specifications and Analytical Methods for Lipitor tablets manufactured at the Vega Baja facility
- Batch analysis summary for lots of Lipitor tablets manufactured at Vega Baja
- Completed batch records for the stability batches manufactured in Vega Baja
- Comparative dissolution profiles for stability batches manufactured in Vega Baja and process validation batches manufactured in Freiburg
- Three months room temperature [redacted] and accelerated [redacted] stability data for Lipitor tablets manufactured at Vega Baja and Freiburg

Should you have any questions regarding this submission, please contact me at 313/996-7596 or FAX 313/996-7890 or Dr. Phil Simonson at313/996-5781.

734 c22 7596

REVIEWS COMPLETED
AP kra 8/4/98
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
mas 8/4/98
CSO INITIALS DATE

734 → 734 c22 5781

Sincerely,

Sean Brennan

Sean Brennan
Senior Director
Worldwide Regulatory Affairs

SB\ps\rm
t:\nda\20-702\012898-60

Attachments

Desk Copy: Ms. Diana Amador, San Juan FDA District Office
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-011

FEB 13 1998

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

Attention: Sean Brennan, 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-011

Date of Supplement: February 9, 1998

Date of Receipt: February 10, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on April 11, 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-011
HFD-510/Div. Files
HFD-510/CSO/M. Simoneau

filename: C:\DATA\WPFILES\20702ACK.

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

`ER 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
Mary E Taylor	Director Worldwide Regulatory Affairs	February 9, 1998