

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20702/S002

Trade Name: LIPITOR TABLETS

Generic Name: ATORVASTATIN CALCIUM

Sponsor: PARKE-DAVIS

Approval Date: 11/28/97

INDICATION(s): LIPID LOWERING AGENT IN HUMANS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20702/S002

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20702/S002

APPROVAL LETTER

NDA 20-702/S-002

OCT 28 1997

Parke-Davis
Attention: Margaret J. Uprichard, Pharm.D.
2800 Plymouth Rd.
P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Dr. Uprichard:

Please refer to your supplemental new drug application dated July 7, 1997, received July 8, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lipitor (atorvastatin calcium) tablets.

The supplemental application provides for changes to be made to the CLINICAL PHARMACOLOGY section of the label. The volume of distribution was originally reported as 565 liters and the absolute bioavailability was 12%. After recalculation the volume of distribution is 381 liters and the bioavailability is 14%.

We have completed the review of this supplemental application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted draft labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted July 7, 1997.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 20-702/S-002. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

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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, Project Manager, at (301) 827-6418.

Sincerely yours,

/s/ 10-28-97

Solomon Sobel, M.D.

Director

Division of Metabolic and Endocrine Drug
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-702/S-002

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cc:

Original NDA 20-702

HFD-510/Div. files

HFD-510/CSO/M.Simoneau

HFD-510/C.Jones/H.Ahn/D.Orloff

DISTRICT OFFICE

HF-2/Medwatch (with labeling)

HFD-92/DDM-DIAB (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.

HFD-560/OTC (with labeling - for OTC Drug Products Only)

HFI-20/Press Office (with labeling)

Drafted by: MAS/October 24, 1997/wp20702.002

Initialed by: C.Jones 10.27.97/H.Ahn 10.27.97/X.Ysern 10.27.97/S.Moore

10.27.97/E.Barbehenn 10.27.97/R.Steigerwalt 10.27.97/D.Orloff 10.27.97/E.Galliers
10.27.97

final: Mas 10.28.97

APPROVAL (AP)

**APPEARS THIS WAY
ON ORIGINAL**

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20702/S002

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

SEP 23 1997

Clinical Pharmacology & Biopharmaceutics Review

NDA: 20-702

SUBMISSION DATE: July 7, 1997

BRAND NAME: LIPITOR®

GENERIC NAME: Atorvastatin

REVIEWER: Carolyn D. Jones, Ph.D.

SPONSOR: Parke-Davis Pharmaceutical Research
Ann Arbor, Michigan

Type of Submission: Labeling Supplement

SYNOPSIS:

Atorvastatin (CI-981), a synthetic inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, is used as a lipid-lowering agent in humans. The enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is the rate-limiting step in the biosynthesis of cholesterol. The drug is recommended for use in patients with hypercholesterolemia (heterozygous familial and nonfamilial), mixed dyslipidemia and homozygous familial hypercholesterolemia. Atorvastatin tablets for oral administration will be marketed as 10, 20 or 40 mg tablets and the ^{recommended} dose is 10 to 80 mg once daily taken any time of day, with or without food.

This submission references the Final Printed Labeling dated February 10, 1997. The original pharmacokinetic analysis was determined using data points that

detection. A few of the data points fell below the limit of

As a result, the sponsor is requesting that changes be made to the CLINICAL PHARMACOLOGY section of the label. The volume of distribution was originally reported as 565 liters and the absolute bioavailability was 12%. After recalculation the sponsor reported the volume of distribution as 381 liters and the bioavailability as 14%.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the current submission and approves the sponsor's request to change the label.

**APPEARS THIS WAY
ON ORIGINAL**

/S/

9/22/97
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II

/S/

RD/FT initialed by Hae Young Ahn, Ph.D., Team leader

9/23/97

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

"CM"

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20702/S002

CORRESPONDENCE

Pharmaceutical
Research

2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

~~NDA SUPPLEMENT ORIGINAL~~

NDA NO. _____ REF. NO. _____

July 7, 1997 NDA SUPPL FOR _____

NDA 20-702
Ref. No. 39
Lipitor™ (atorvastatin calcium) Tablets

Re: Labeling Supplement



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 approved NDA 20-702 for Lipitor™ (atorvastatin calcium) Tablets and our Final Printed Labeling submitted February 10, 1997.

It has come to our attention that the pharmacokinetic parameters of volume of distribution and absolute bioavailability are incorrectly reported in the CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism, subsection as 565 liters and 12%, respectively, in the Final Printed Labeling. These values were supported by the following research report:

"An Absolute Bioavailability Study of Atorvastatin (Protocol 981-030)", by DM Gibson, RH Stern, Whitfield LR, dated March 28, 1996 (Research Report No. 744-00265) located in NDA Volume 1.174, Page 121.

The original pharmacokinetic analysis for this study

The pharmacokinetic parameters for subjects with these detectable concentrations have been recalculated. The correct values for the volume of distribution and absolute bioavailability are 381 liters and 14%, respectively. The research report has been revised to incorporate these corrections, and the corrected version is included behind Tab 1.

Therefore, in accordance with 21 CFR 314.70(b)(3), we are submitting for your review and approval a revised package insert (Tab 2). This package insert will not be used in production until approved by the Division.

Sobel
IS/
7/9/97

APPEARS THIS WAY
ON ORIGINAL

Noted
The Chemistry of the
related sections of the
package insert have
not been modified
IS/
7/9/97

Solomon Sobel, M.D.
NDA 20-702
July 7, 1997
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APPEARS THIS WAY
ON ORIGINAL

If there are any questions or comments regarding this submission, please contact me at 313/996-4906 or FAX 313/998-3283.

REVIEWS COMPLETED	
CSO ACTION: <i>A Plan</i> <i>10/28/97</i>	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS: <i>/S/</i>	DATE: <i>10/30/97</i>

Sincerely,

Margaret J. Uprichard

Margaret J. Uprichard, Pharm.D.
Manager, FDA Liaison
Worldwide Regulatory Affairs

MU/rp
t:\nda\20-702\070797-39

Attachments

Desk Copy: Dr. Carolyn Jones (HFD-510)

MSD
/S/
1-18-97
/S/
1-18-97

APPEARS THIS WAY
ON ORIGINAL