

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20702/S004

Trade Name: LIPITOR TABLETS

Generic Name: ATORVASTATIN CALCIUM

**Sponsor: PARKE-DAVIS PHARMACEUTICAL
RESEARCH**

Approval Date: 02/02/98

Indication(s): TREATMENT OF HYPERCHOLESTEROLEMIA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20702/S004

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Medical Review(s)	X			
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

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Application Number: 20702/S004

APPROVAL LETTER

FEB 2 1998

NDA 20-702/S-004

Parke-Davis Pharmaceuticals Research
Division of Warner-Lambert Company
Attention: Irwin Martin, Ph.D.
2800 Plymouth Road
Ann Arbor, MI 48106-1047

Dear Dr. Martin:

Please refer to your supplemental new drug application dated July 17, 1997, received July 18, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lipitor (atorvastatin calcium) tablets.

We acknowledge receipt of your submissions dated December 3, 1997, and December 12, 1997.

The supplemental application provides for a change in the package insert to remove the requirement for monitoring liver function tests at week 6 of treatment under the WARNINGS/ "Liver Dysfunction" section of the label.

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 draft labeling in the submission dated December 3, 1997. 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 on December 3, 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-004. 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

APPEARS THIS WAY
ON ORIGINAL

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,

/S/ 2 | 2 | 98

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

cc:

Original NDA NDA 20
HFD-510/Div. files
HFD-510/CSO/M. Simoneau
HFD-510/D. Orloff/E.Barbehenn/X.Ysern
DISTRICT OFFICE
HF-2/Medwatch (with labeling + MOR)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling + MOR)
HFI-20/Press Office (with labeling)

Drafted by: Mas/January 30, 1998/20702.4

Initialed by:D.Orloff1.30.98/E.Barbehenn1.30.98/X.Ysern1.30.98/E.Galliers2.2.98

final: Mas 2.2.98

APPROVAL (AP)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20702/S004

MEDICAL REVIEW(S)

NDA 20-702/S-004
Lipitor (atorvastatin calcium) Tablets
Parke-Davis
ref. No. 57

Date of submission: December 12, 1997
Date of review: December 29, 1997

APPEARS THIS WAY

Background

Labeling supplement S-004 was submitted on July 17, 1997 and proposed changes in the recommended schedule of LFT monitoring after initiation of therapy with atorvastatin, dispensing with the 6-week check. Based on the low incidence of clinically important transaminase elevations overall, on the fact that only a small percentage occurred during the first six weeks, it was agreed that the first check could be at twelve weeks after initiation of treatment or elevation in dose. In addition, though, review of the timing of occurrence of persistent LFT changes >3X ULN in patients treated with 80 mg suggested that a significant fraction (6/19, 32%) occurred between weeks 13 and 18. This reviewer suggested that consideration be given to recommending an 18-week LFT check in patients treated with 80 mg. The sponsor has responded with the current submission.

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Current submission

The sponsor has now submitted a reanalysis of the LFT data in which the time to onset (detection) of persistent LFT elevations >3X ULN denotes the duration of exposure at a single fixed dose. This is in contrast to the previous analyses in which the time to onset referred to duration of treatment with atorvastatin, regardless of dose. Thus, a persistent LFT elevation at week 12 in a patient treated with 80 mg (for 8 weeks) after 4 weeks of treatment at a lower dose would be recorded as occurring on 80 mg after 12 weeks of exposure. In the current analysis, this case would be marked at the 8-week time point. Indeed, this latter analysis is in keeping with recommendations to check LFTs before the initiation of therapy and elevation in dose. Finally, according to the sponsor, "the occurrence or lack of occurrence of a persistent transaminase elevations during treatment with one atorvastatin dose is not predictive of effects on [sic] another dose. This last fact serves as rationale for rechecking LFTs after any elevation in dose.

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The current analysis is of data from 3581 patients exposed to atorvastatin in 9 completed and 2 ongoing studies for whom complete information on dose, treatment schedule, and duration of therapy are available. The exposure for at least one year (48 weeks) across the dosage range includes 1196, 177, 65, and 544 patients treated with 10, 20, 40, and 80 mg atorvastatin, respectively. The corresponding numbers for exposures of at least 2 years (108 weeks) are 95, 3, 2, and 98 patients.

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Of the 3581 patients included in the analysis, 31 (0.9%) developed persistent LFT elevations >3X ULN. All occurred in the first 48 weeks of treatment. By dose, there were 3, 2, 5, and 21 patients each taking 10, 20, 40, and 80 mg, respectively.

The timing of these elevations, by dose, relative to initiation of therapy at that dose, is shown in the table below. The numbers of patients exposed are shown in parentheses.

Weeks of exposure	Time on dose at onset of persistent LFT elevation by dose							
	0-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48
10mg		1				1		1
	(2299)*	(2113)	(1882)	(1529)	(1318)	(1274)	(1255)	(1220)
20mg		1				1		
	(1117)	(874)	(662)	(578)	(552)	(529)	(354)	(248)
40mg	1	2	1			1		
	(1070)	(611)	(509)	(398)	(366)	(311)	(260)	(149)
80mg	1	13	2	1	3			1
	(1108)	(1011)	(950)	(841)	(803)	(760)	(706)	(657)

* number of patients exposed

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This analysis reconfirms that this is a problem largely of the 80 mg dose. Furthermore, the majority (14/21) of the persistent LFT elevations are detected between 0 and 12 weeks of therapy at that dose. Finally, only one case occurred in the first 6 weeks of treatment. Thus, waiting until week 12 for the first LFT check should present little if any risk to patients.

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From week 13 on, the cases are infrequent and are spread relatively evenly across exposure intervals. Indeed, if the second check were 3 to 6 months later (at week 24 or 36), nearly all the cases would have been detected.

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Conclusions and recommendations

- 1) No 18-week LFT check need be recommended in labeling.
- 2) The long-term, controlled exposure to atorvastatin is inadequate to recommend dispensing with long-term monitoring of LFTs at this time.

APPEARS THIS WAY
ON ORIGINAL

David G. Orloff, M.D.
Medical Team Leader
DMEDP/CDER/FDA

cc:
NDA 20-702
HFD-510
HFD-510: Simoneau

/S/
12-30-97

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ON ORIGINAL

SEP 17 1997

NDA 20-702

ref. No. 41

LIPITOR (atorvastatin calcium) Parke-Davis

Labeling supplement proposing change in recommendations for LFT monitoring

Date of submission: July 17, 1997

Date of review: September 15, 1997

APPEARS THIS WAY
ON ORIGINAL**Introduction**

This supplement proposes a change in the recommended LFT monitoring that would dispense with the 6-week LFT check. The sponsor proposes that monitoring would still be recommended "before the initiation of treatment, after 12 weeks of therapy or elevation in dose, and periodically (e.g., semiannually) thereafter." This proposal follows on approved revisions to the labeling for ZOCOR and PRAVACHOL based on data from 4S and WOSCOPS, respectively. For those two drugs, the availability of data from large-scale, long-term, placebo-controlled trials provided information on the overall risk of significant transaminase elevations, as well as on the predictive value of normal or abnormal LFTs before the initiation of treatment or early in the course of therapy for subsequent persistent transaminase elevations $>3 \times \text{ULN}$. In WOSCOPS, the dose used was 40 mg, which is the highest approved dose, and in 4S, one third of the patients were treated with 40 mg, the highest approved dose, and two thirds with 20 mg. In both studies, the overall rates of significant LFT abnormalities were very low ($\leq 1\%$) and not different across treatment groups, and furthermore, a normal value at baseline (4S) or early in therapy (4S, WOSCOPS) predicted a very low risk of a subsequent abnormality of presumed clinical significance.

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In this application, the data in support of the proposed changes are derived from the original NDA for atorvastatin and include information in the 4-month safety update. The exposure to atorvastatin included 4271 patients treated in clinical trials with treatment duration out to two years. While the long-term safety with regard to the liver has not been demonstrated for this drug, and while the limited exposure therefore underestimates the true incidence of significant transaminase elevations, the NDA data do permit conclusions as to, at the least, a first phase of LFT elevations that occurs fairly early in treatment, detected between 7 and 18 weeks after initiation of therapy. Furthermore, the NDA data do provide information about the severity of the hepatic reactions to atorvastatin, the existence of dose-dependency, and therefore permit reasoned judgement about the risk of waiting until week 12 before rechecking the LFTs.

APPEARS THIS WAY
ON ORIGINAL**Review of the data submitted**

The overall rate of clinically important transaminase elevations (persistent $>3 \times \text{ULN}$) was low (30/4271, 0.7%) among atorvastatin treated patients. Approximately half (14/30) of such patients either discontinued or interrupted treatment (1 patient) and roughly one third or those remaining on drug (5/16) were able to continue without a reduction in dose.

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ON ORIGINAL

One patient developed jaundice, and 9 patients had levels at the last available assessment that remained above the ULN.

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With regard to the timing of detection of the persistent LFT elevation, in 24/30 (80%) the persistent elevations were detected at or after 12 weeks of treatment. Relevant to the proposed labeling, assuming a first on-treatment screen at 12 weeks, 11/30 (37%) of cases would be detected. Six patients (20%) had elevations that were manifest earlier than the week 12 time point. Of these, 2 had a first occurrence between 0 and 6 weeks of therapy. The 30 patients are listed in the Attachment A reproduced from the sponsor's submission. Attachment B (also the sponsor's) contains the medical narratives for the 6 patients with persistent LFT elevations in the first 11 weeks of treatment. Of note is the fact that 4 were on 80 mg daily, and that in all the transaminase elevations appeared related to drug, even if several of the patients may have had an identifiable predisposing risk factor for adverse hepatic reaction.

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ON ORIGINAL

Table 1 below shows the incidence of persistent transaminase elevations by dose and by weeks of treatment.

Table 1. Persistent LFT elevations >3 X ULN by dose and duration of exposure. NDA 20-702

Ator dose	10 mg	20 mg	40 mg	80 mg
weeks on drug				
0-6	0	0	1	1
7-12	1	0	1	7
13-18	0	0	0	6
19-24	0	1	1	2
25-30	0	0	1	0
31-36	1	0	0	2
>36	1	2	1	1
total cases	3	3	5	19

APPEARS THIS WAY

APPEARS THIS WAY

What is clear is that without the 6-week LFT check, in the NDA studies, the discovery of persistent LFT elevations in 2 patients would have had to wait until the 12-week check. (Another three patients with elevations manifest at weeks 7 and 8 would also have waited, though this would be the case under the current recommended screening protocol.) What is also evident is that among the group with elevations in the first 12 weeks, 8 of 11 were treated with the 80 mg dose. Indeed, overall, nearly 2/3 of the cases were seen in patients treated with the 80 mg dose. In addition, note the 6 cases in the 80 mg group who would be picked up with an 18-week screen. Finally, note that overall as well as in the 80 mg group, a 36-week test (which is roughly 6 months after the 12-week screen) brings the total "capture" rate for LFT abnormalities to 25/30 or 84% (18/19 for the 80 mg group). It is known that the incidence of persistent LFT elevations is

greatest for the 80 mg group. This information is already included in the label. The data above do suggest, however, that there may be utility to at least one extra LFT check in patients treated with 80 mg (ie, at 18 weeks).

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Conclusions

Atorvastatin therapy is associated in a small percentage of cases (0.7% overall) with persistent elevations in serum transaminases to >3X ULN. At the highest approved dose (80 mg), the rate was 2.3% in the NDA trials. Of the 30 cases in the NDA, one developed jaundice, while none of the others had signs or symptoms. In addition, at least 7 (including the jaundiced patient) had other factors active either causing the abnormalities or perhaps predisposing to the reaction to drug. These factors included elevated baseline LFTs, elevated baseline bilirubin, hepatitis, mononucleosis, alcohol consumption, paracetamol use, and acetaminophen use. While 9 patients had elevations at the last assessment, none was >3 X ULN, and only two of the 9 discontinued treatment. In sum, the hepatic reactions to atorvastatin to date have been benign.

APPEARS THIS WAY
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An LFT treatment protocol which involves a screen pretreatment and prior to any elevation in dose (and excludes patients with persistent elevations-per CONTRAINDICATIONS) and a 12-week test will miss a few cases of significant LFT elevations. In the experience presented, 2/30 (6.6%) cases occurred between 0 and 6 weeks after initiation of therapy. Assuming all of the 4271 patients were exposed for at least six weeks, these two cases represent an overall rate in the first six weeks of 0.05%. The hepatic reactions to atorvastatin have been benign to date, and the 6-week test is not justified based on the very poor yield predicted from the data available and the minimal risk of delaying the first post-treatment LFT check until 12 weeks.

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ON ORIGINAL

While a screening protocol involving a 12-week and a 36-week (roughly 6 months later) check of the LFTs would miss few early abnormalities and ultimately pick up the vast majority who would be expected over a two-year exposure to develop LFT elevations to >3X ULN, at least for the 80 mg group in the NDA studies, 6/19 (32%) of the cases occurred between 13 and 18 weeks. It seems reasonable based on these data to recommend an 18 or 24-week check for patients treated with that dose.

APPEARS THIS WAY
ON ORIGINAL

Recommendations

This supplement should be approved pending the sponsor's response to the comments that follow below.

APPEARS THIS WAY
ON ORIGINAL

To be conveyed to the sponsor:

1) Please include information preceding the recommended LFT testing protocol about the number and percent of cases with persistent LFT elevations who developed the abnormalities by week 12 of treatment in order to convey the yield of a test at that point.

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ON ORIGINAL

2) Please change the wording of the LFT monitoring recommendation to the following: It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.

3) Please also include language recommending an additional LFT screen at 18 or 24 weeks for patients treated with the 80 mg dose.

David G. Orloff, M.D.
Medical Team Leader
DMEDP/CDER/FDA

cc:
NDA 20-702
HFD-510
HFD-510: Simoneau/Orloff

9.17.97

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT A. Listing of Atorvastatin-Treated Patients Who Had Persistent Liver Transaminase Elevations >3 x ULN

APPEARS THIS WAY
ON ORIGINAL

TABLE 1. Patients With Persistent Transaminase Elevations >3 x ULN in Atorvastatin-Treated Patients^a

Study	Center	Patient	Atorvastat in Dose Mg Once Daily	Weeks on Drug at Onset of Event	Action Taken	Transaminase Value Last Assessment (U/L)	Relationship ^b /History
4	1	16	40	7	Discontinued (end of study)	NI	NI /Hepatitis
8	17	7	10	10	Discontinued		Unlikely/Elevated baseline levels
25	3	11	80	12	Discontinued		Probably/None
25	3	23	80	12	Discontinued		Probably/None
25	4	5	80	8	Discontinued		Possibly/None
25	4	24	80	8	Discontinued		Possibly/None
56	1	203	80	12	Reduced Dose		NI/None
56	2	147	80	23	Reduced Dose		NI/None
56	2	165	80	12	Discontinued		NI/Gall Stones
56	4	111	80	12	Reduced Dose		NI/None
56	6	124	20	20	Discontinued		NI/None
56	6	130	80	32	Reduced Dose		NI/None
56	12	114	80	52	Discontinued		Probably/None
56	12	115	40	4	Discontinued		Unlikely/Mononucleosis
56	17	208	40+ Colestipol	52	Reduced Dose		Probably/None
56	18	113	80	16	Reduced Dose		NI/None
56	19	210	80	16	Reduced Dose		NI/None
57	7	1	10	36	Discontinued		Unlikely/Hepatitis A
57	2	24	40	26	Reduced Dose		Probably/Concurrent paracetamol
62	4	46	10	76	Interrupt		Possibly/None
62	31	6	20	43	Reduced Dose		Possibly/None
68	2	106	80	5	Reduced Dose		Probably/Cholecystitis
68	22	105	80	15	No Change		Possibly/None
77	1	5	40	60	No Change		Unlikely/Elevated baseline bilirubin and alcohol consumption
77	1	6	80	16	No Change		Unlikely/ Concurrent acetaminophen
77	6	18	80	16	Discontinued		Probably/Gall stones
77	6	32	20	47	Reduced Dose		Probably/None
77	9	13	80	20	No Change		Probably/None
77	17	8	80	15	Discontinued		Definitely/None
77	6	33	80	35	No Change		Possibly/None

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT B. Medical Narratives for 6 Patients Who Experienced Persistent Liver Transaminase Elevations >3 x ULN in the First 11 Weeks of Treatment

Patient 16 (Study 981-004, Center 001), a 64-year-old white man (with dyslipidemia) and a history of serum hepatitis 22 years earlier, had

at the final visit (Day 46) of the study. Two days later (Day 48) these values had decreased to

At a follow-up laboratory measurement on Day 63, both values had decreased to

The patient was taking concomitant vitamin supplements. This patient had taken 40 mg atorvastatin during the study.

Patient 007 (Study 981-008, Center 017), a 45-year-old Hispanic man with hypercholesterolemia and a history of mildly elevated liver function tests, had an AST level of on Day 71 of treatment with atorvastatin 10 mg QD. Study medication was discontinued on Day 77. No concomitant medications were used at the time of the event. He had mildly elevated transaminase levels and the first 2 visits of baseline (Visit 1 through Visit 4).

At Visit 5, the randomization visit or the last value prior to double-blind, the ALT value

The patient was unable to return to the clinic until Day 29. The ALT value 4 days after discontinuation of study medication. The patient was asymptomatic and denied the use of alcohol or a history of drug abuse. At the follow-up visit on Study Day 375, the patient's ALT level was in the normal range

The patient recovered. The investigator considered this event moderate in intensity and unlikely related to study medication.

Patient 005 (Study 981-025, Center 004), a 64-year-old white woman with a history of hypercholesterolemia, had an on Day 58 of treatment with 80 mg atorvastatin QD. The patient did not report any complaints and continued study medication. The ALT was reassessed and was on Day 65. The patient discontinued study medication and was withdrawn from the study on Day 64. The patient returned to the clinic for follow-up measurements and the ALT level returned to normal on Day 86. The investigator and the sponsor considered the event moderate and possibly related to study medication.

Patient 024 (Study 981-025, Center 004), a 52-year-old white man with hyperlipidemia and a history of hernial repair and vasectomy, had an

on Day 56 of treatment with 80 mg atorvastatin QD. The patient discontinued study medication on Day 55. A follow-up visit revealed an however, another follow-up measurement on Day 78 revealed an ALT level within the normal range. The investigator and the sponsor considered the event moderate and possibly related to study medication.

Patient 115 (Study 981-056, Center 012), a 37-year-old white man with history of familial hypercholesterolemia, experienced elevated liver enzymes beginning Day 29 after receiving atorvastatin 40 mg QD for 29 days. On Day 29 the dose of atorvastatin was titrated to 80 mg QD and his ALT level was (). Study medication was discontinued on Day 30. An ALT level rechecked on Day 31 was and the patient was discontinued from the study. An ALT level rechecked on Day 72 had returned to normal . The investigator considered the increased transaminase levels unlikely related to atorvastatin therapy since the patient screened positive for mononucleosis at the time of the elevations.

APPEARS THIS WAY
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Patient 106 (Study 981-68, Center 002), a 57-year-old white man with a history of hyperlipidemia, hypertension, and esophagitis, developed increased transaminase levels while receiving atorvastatin 80 mg QD. Total exposure to atorvastatin 80 mg QD was 35 days. Concurrent medications include alprazolam, captopril, and ranitidine. The patient reported no alcohol use. Labs were measured again on Study Day 46

Study medication was interrupted on Day 48.

On Study Day 58, the levels normalized

A reduced dose of atorvastatin 40 mg QD was started on Study Day 60. On Day 78, transaminase levels were slightly elevated

On Day 109, the patient reported epigastric-type pain and discomfort and was referred to his primary-care physician. On Day 110, he was admitted to the hospital and underwent a cholecystectomy. Postoperative diagnosis was gangrenous cholecystitis. Liver function tests performed in the emergency room were reported to be within normal limits. The investigator considered this event probably related to study medication.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20702/S004

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE



Food and Drug Administration
Rockville MD 20857

NDA 20-702/S-004

PARKE-DAVIS PHARMACEUTICALS RESEARCH
DIVISION OF WARNER-LAMBERT COMPANY
2800 Plymouth Road,
ANN ARBOR, MI 48105

JUL 23 1997

Attention: Irwin G. Martin, Ph. D., Vice President, FDA Liaison, Worldwide Regulatory Affairs

Dear Dr. Martin:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: LIPITOR (atorvastatin calcium) Tablets

NDA Number: 20-702

Supplement Number: S-004

APPEARS THIS WAY
ON ORIGINAL

Date of Supplement: July 17, 1997

Date of Receipt: July 18, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 16, 1997, 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

APPEARS THIS WAY
ON ORIGINAL

Sincerely /S/

APPEARS THIS WAY
ON ORIGINAL

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

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NDA 20-702/S-004

Page 2

cc:

Original NDA 20-702/S-004

HFD-510/Div. Files

HFD-510/CSO/M. Simoneau

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filename:

SUPPLEMENT ACKNOWLEDGEMENT

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ORIGINAL

Pharmaceutical
Research

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

NDA NO. 20-702 REF. NO.

NDA SUPPL FOR



July 17, 1997

NDA 20-702

Ref. No. 41

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



APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Sobel:

Reference is made to our approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets, the 4-month safety update to this NDA submitted October 16, 1996 (Ref. No. 14)

At this time we are requesting a re-consideration of data presented in the NDA to allow for this change. A proposal which includes the rationale for this change and a brief data summary is found in Attachment A. The proposed change to the labeling is found in Attachment B.

This labeling supplement contains no new clinical data. Therefore, a user fee is not required.

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

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ON ORIGINAL

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ON ORIGINAL

Handwritten: Notice /S/ 8/4/97

REVIEWS COMPLETED	
<i>7/22/97 2/12/97</i>	
ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> M.A.I.
<input type="checkbox"/> MEMO	
<i>/S/</i>	<i>9/12/97</i>
CSO INITIALS	DATE

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Handwritten signature: Margaret J. Uprichard

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

MU\rm t:\nda\20-702\071797-41
Attachment

cc: Dr. David Orloff (HFD-510)

Handwritten notes:
Maybe this should be based on the dose?
Will add this in my review.
Will review dest copy.
Initials: /S/ 8-1-97



NDA SUPPLEMENT

December 3, 1997

NDA 20-702
Ref. No. 52
Lipitor® (atorvastatin calcium) Tablets

APPEARS THIS WAY
ON ORIGINAL

Re: Labeling Supplement S-004

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

APPEARS THIS WAY
ON ORIGINAL



Dear Dr. Sobel:

Will review reasons for these decisions on receipt of info from sponsor. 12/10/97

Reference is made to our approval NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets; to our labeling supplement (S-004) submitted July 17, 1997; to Dr. David Orloff's fax comments on our proposal received September 29, 1997.

Listed below in *italic* type are Dr. Orloff's comments, followed by the resolution reached during the teleconference:

APPEARS THIS WAY
ON ORIGINAL

12/10/97 /S/

- 1. *Please include information preceding the recommended LFT testing protocol about the number and percent of cases with persistent LFT elevations who developed the abnormalities by week 12 of treatment in order to convey the yield of a test at that point.*

APPEARS THIS WAY
ON ORIGINAL

It was agreed that it would not be necessary to add this information to the labeling.

- 2. *Please change the wording of the LFT monitoring recommendation to the following: It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.*

APPEARS THIS WAY
ON ORIGINAL

A copy of the revised labeling incorporating this exact wording is attached.

Enclosed Labeling acceptable 1-29-98 /S/

APPEARS THIS WAY
ON ORIGINAL

Solomon Sobel, M.D.
NDA 20-702
December 3, 1997
Page 2

3. Please also include language recommending an additional LFT screen at 18 or 24 weeks for patients treated with the 80 mg dose.

It was agreed that it would not be necessary to add this language to the labeling.

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

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

APPEARS THIS WAY
ON ORIGINAL



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

MU\rm
t:\nda\20-702\120397-52

Attachment

Desk Copy: Dr. David Orloff (HFD-510)

REVIEWS COMPLETED	
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

APPEARS THIS WAY
ON ORIGINAL



December 12, 1997

NDA 20-702

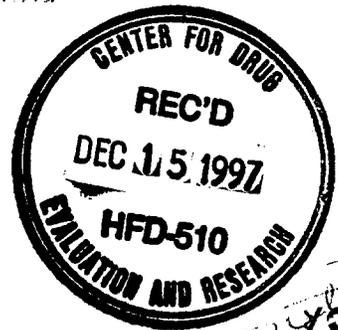
Ref. No. 57

Lipitor® (atorvastatin calcium) Tablets

Re: Labeling Supplement S-004:
Response to Request for Information

APPEARS THIS WAY
ON ORIGINAL

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



Review completed 1-2/98

4/5/98

Dear Dr. Sobel:

APPEARS THIS WAY
ON ORIGINAL

Reference is made to our approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets; to our labeling supplement (S-004) submitted July 17, 1997; to Dr. David Orloff's fax comments on our proposal received September 29, 1997; and to our November 26, 1997 teleconference with Dr. Orloff to discuss his comments. During the teleconference we discussed Dr. Orloff's third comment in the fax ("Please also include language recommending an additional LFT screen at 18 or 24 weeks for patients treated with the 80 mg dose."). It was pointed out that the pattern of LFT elevations in the atorvastatin clinical studies database showed an apparent shift in the timing of the onset of LFT elevations to weeks 13 through 18 for patients receiving atorvastatin 80 mg/day; however, it should be noted that these patients were "up-titrated" to this dose.

At Dr. Orloff's request, we are submitting additional data analyses discussed during the teleconference. When one examines time on an individual dose, this pattern shifts downward such that the majority of patients receiving atorvastatin 80 mg with LFT elevations declare themselves by Week 12.

APPEARS THIS WAY
ON ORIGINAL

Solomon Sobel, M.D.
NDA 20-702
December 12, 1997
Page 2

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:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> M.A.I. <input type="checkbox"/> MEMO
/S/	
CSO INITIALS	DATE

Sincerely,

Margaret J. Uprichard

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

MU\rm
t:\nda\20-702\121297-57

Attachment

Desk copy: Dr. David Orloff (HFD-510)

APPEARS THIS WAY
ON ORIGINAL

DEC 30 1997

To: Parke-Davis
Attention: Ms. Margaret J. Uprichard, R.Ph.
Fax: 313-998-3283

Ref: NDA 20-702, (labeling supplement S-004) for
Lipitor™, submission dated December 12, and fax dated December 2,
1997.

In regard to the submission and fax mentioned above, we have the
following comments:

1. No 18-week LFT check need be recommended in the labeling.
2. The long-term, ~~the~~ controlled exposure to atorvastatin is inadequate to recommend dispensing with long-term monitoring of LFT's at this time.

This information was faxed to Margaret Uprichard on December 30,
1997.

IS/10

12/30/97

~~Gene~~ M. Weber, CSO
(for Peggy Simoneau)

APPEARS THIS WAY
IN ORIGINAL

CLEARED FOR FAXING

IS/

12-30-97

David Orloff, M.D.

APPEARS THIS WAY
IN ORIGINAL

CC: Original NDA 20-702
Div File
HFD 510/D Orloff