CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020702/S003 and 020702/S005

CHEMISTRY REVIEW(S)

Simoneau
AUG 25 1997

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 SEI-005
Doc. 22-JUL-1997 Rec. 23-JUL-1997

5. Name of the Drug Lipitor Tablets

6. Nonproprietary Name
Atorvastatin Calcium

7. SUPPLEMENT PROVIDES the treatment of patients with Fredrickson Type III hyperlipoproteinemia.

8. AMENDMENT
Doc. 14-AUG-1997 Rec.15-AUG-1997

9. PHARMACOLOGICAL CATEGORY Lipid Modifier.
HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.

10. HOW DISPENSED Rx

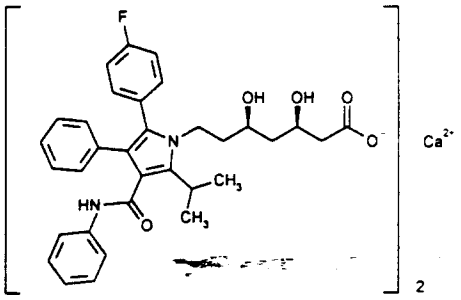
11. RELATED -N. A.-

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 This supplement, S-005 (reference Nº 42) provides for the use of Lipitor (atorvastatin calcium) Tablets for the treatment of patients with Fredrickson Type III hyperlipoproteinemia. The indication for patients with Fredrickson Types IV and V was given in supplement S-003. **Drug Substance and Drug Product remain unchanged.** As indicated , the addition of this indication do not significantly increase the marketing forecasts for the drug, so the previously submitted and approved Environmental Assessment information is not effected.

16. CONCLUSIONS AND RECOMMENDATIONS From the chemistry viewpoint this supplement can be approved.

17. REVIEWER NAME (AND SIGNATURE)
Xavier Ysern, PhD
/S/

DATE COMPLETED 19-AUG-1997

R/D INITIATED BY

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ON ORIGINAL

Simonea
AUG 25 1997

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 SEI-003
Doc. 16-JUL-1997 Rec. 17-JUL-1997

5. Name of the Drug Lipitor Tablets

6. Nonproprietary Name
Atorvastatin Calcium

7. SUPPLEMENT PROVIDES the treatment of patients with Fredrickson Type IV and V hyperlipoproteinemia.

8. AMENDMENT
Doc. 14-AUG-1997 Rec. 15-AUG-1997

9. PHARMACOLOGICAL CATEGORY Lipid Modifier.
HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.

10. HOW DISPENSED Rx

11. RELATED -N. A.-

12. DOSAGE FORM Tablet

13. POTENCY 10, 20 and 40 mg

14. CHEMICAL NAME AND STRUCTURE
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$(C_{33}H_{34}FN_2O_5)_2Ca$
FW (anhydrous calcium salt) 2 x 557.7 + 40.0 = 1155.38
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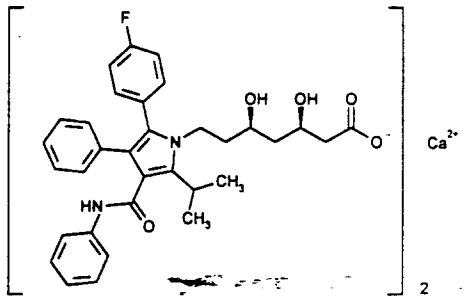
[*R*-(*R**,*R**)]-2-(4-flourophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrole-1-heptanoic acid calcium salt (2:1)



15. COMMENTS This supplement, S-003 (reference Nº 40), provides for the use of Lipitor (atorvastatin calcium) Tablets for the treatment of patients with elevated serum triglyceride levels, Fredrickson Type IV and V, who present a risk for pancreatitis. The indication for patients with Fredrickson Types III is given in supplement S-005. **Drug Substance and Drug Product remain unchanged.** As indicated the addition of this indication do not significantly increase the marketing forecasts for the drug, so the previously submitted and approved Environmental Assessment information is not effected.

16. CONCLUSIONS AND RECOMMENDATIONS From the chemistry viewpoint this supplement can be approved.

17. REVIEWER NAME (AND SIGNATURE)
Xavier Ysern, PhD /S/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020702/S003 and 020702/S005

STATISTICAL REVIEW(S)

NDA 20-702
Lipitor

June 15, 1998
Parke-Davis

Review and Evaluation of Clinical Data
Submissions dated July 22, 1997 and April 27, 1998; S-005

Materials Reviewed: Vol 1 and amendment

1 Background

1.1 Introduction

This supplement to the atorvastatin original NDA seeks approval for the use of atorvastatin (a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) as a lipid-lowering agent to be employed in patients with hypertriglyceridemia who do not respond adequately to diet and who have Fredrickson type III hyperlipoproteinemia (dysbetalipoproteinemia; dyslipidemia; familial or primary dysbetalipoproteinemia).

Type III hyperlipoproteinemia (Fredrickson) is uncommon and occurs in approximately 1 in 10,000 individuals; it is transmitted by a single gene mechanism with variable penetrance. Pts with this genetic abnormality have an abnormal apo E protein that results in elevated total plasma cholesterol and triglyceride concentrations, secondary to an increase in VLDL remnants and accumulation of chylomicron remnants and intermediate-density lipoproteins (IDLs). These patients are generally homozygous for the apolipoprotein (apo) E2 that is removed from the chylomicron particle in order to allow catabolism of the VLDL remnant. Even though the apo E2 of homozygous E2 patients has a low affinity for the LDL receptor, most of these pts have lipid levels within a normal range. Subjects show apo E_2/E_2 phenotype and TC = or > than 260 mg/dL.

Patients with both the E2/E2 phenotype and associated metabolic abnormalities, such as obesity, DM, hypothyroidism, or other genetic disorders, have impaired remnant clearance; such abnormalities increase VLDL and IDL formation. Pts with this disorder are at increased risk for premature development of both coronary and peripheral vascular disease.

Patients affected with dysbetalipoproteinemia "usually require some form of lipid-lowering therapy in combination with diet modification." Fibrates and HMG-CoA reductase inhibitors (HMGRI) are "the usual therapy" for patients with type III hyperlipoproteinemia; at the present time, gemfibrozil and simvastatin are the respective most effective fibrate and HMGRI marketed for this dyslipidemia.

1.2 Atorvastatin for this and other indications

Atorvastatin is already approved for use as an adjunct to diet to reduce elevated total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), and triglyceride (TG) levels in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb).

1.3 Proposed labeling related to this new indication

This is a proposed new indication for this drug which has been already approved and is presently marketed for other indications. Proposed revised labeling adds the new indication, includes conditions and dosage for use in this new indication, and adds to Clinical Studies (under Clinical Pharmacology) a brief description of the results achieved from the clinical study performed in pts having this disorder and diagnosis.

2 Clinical Data Sources

The sponsor has conducted one new trial, Study 981-039, in patients with "confirmed" type III hyperlipoproteinemia; 16 subjects were included. This trial is reported in this present submission of this supplement and will be reviewed briefly in this MOR, with emphasis on efficacy results and resultant (limited) modifications of labeling.

3 Clinical Study

The present subject trial continued for a total of 32 weeks, and was open-label, performed at a single center, and was designed as a 4-way crossover in 16 subjects with confirmed apo E abnormalities of E2/E2 or E2/E3 genotype. Three different study medications were utilized, each given for 8 weeks; since atorvastatin was administered at two dosage levels, 4 regimens were actually encompassed and compared. The resultant 4 drug regimens: atorvastatin 10 mg daily, atorvastatin 80 mg daily, gemfibrozil 600 mg BID, and simvastatin 40 mg QD.

Although specific drugs and dosages were administered under open and known conditions, the treatment sequence itself was randomized, so that 4 different crossover sequences were employed.

3.1 Objective/rationale

Objectives of this study were "to establish the level of beneficial effects" on lipoprotein fractions and apolipoproteins when atorvastatin was given at two daily dosage levels,10 mg and 80 mg administered once per day, and to compare these results to those achieved on gemfibrozil in a total daily dosage of 1200 mg and simvastatin 40 mg QD in pts with confirmed type III hyperlipoproteinemia, "and to evaluate safety" in this pt population.

3.2 Design

As stated previously, study was open, 32 weeks total duration, with all 16 patients receiving the same drugs and dosages; each regimen was given for a total of 8 weeks, with crossover to the next treatment, however, determined in randomized sequence until all 4 study meds had been taken by the subject. The crossover design "allowed intrasubject comparisons of responses" to all 4 treatments. Randomization to 1 of 4

different treatment sequences "provided a method to balance any carryover effects across treatments."

The trial included 3 phases: an optional 4-week Dietary Assessment Phase for patients not currently following a standard lipid-lowering diet, a 4-week Dietary Lead-in Phase during which baseline assessments and entry criteria were established, and the 32-week Treatment Phase of drug administration. Pts shown to meet the eligibility criteria for inclusion at the end of the Dietary Lead-In Phase were then randomized to 1 of the 4 treatment sequences.

3.3 Protocol

3.3.1 Population, Procedures

Subjects considered eligible for this trial were men and women aged with TC ≥250 mg/dL (6.46 mmol/L) and fasting TG ≥315 mg/L (3.55 mmol/L) at either Weeks -4 or -2. Pts were confirmed as apo E2/E2 or E3/E2 with a ratio of VLDL-C/TG >0.3 at screening.

Exclusions:

1) Active liver disease or hepatic dysfunction "based upon the investigator's knowledge of the patient's medical history and assessment of ALT/AST;"
2) Secondary causes of hyperlipoproteinemia "based upon the investigator's knowledge of the patient's medical history and assessment of TSH and HbA_{1c};"
3) Uncontrolled hypertension "based upon assessment of the investigator's knowledge of the patient's medical history."

At the initiation of each phase, pts were given atorvastatin (10 or 40 mg) tabs, gemfibrozil 600 mg tabs, or simvastatin 20 mg tabs, depending on their treatment sequence. They were instructed to take 1 atorvastatin 10 mg tab daily at bedtime, 2 atorvastatin 40 mg tabs daily at bedtime, 1 gemfibrozil 600 mg tab BID with morning and evening meal, or 2 simvastatin 20 mg tabs together each day with the evening meal. The investigator "assessed patient compliance to study medication by inquiry" at each visit to clinic. Pts who were "determined noncompliant during the study" were counseled but were not withdrawn from the trial.

Prohibited Medications or Precautions:

Patients already taking a lipid-regulating drug "were considered for screening" after a 2-week wash-out period. Length of the washout could be reduced "if the investigator deemed it detrimental" to pt's health to be without lipid-regulating Rx for a 2-week period. If pt had been on the drug probucol, this had to be stopped for a duration of at least 6 months in order for patient to be eligible. Other agents "known to affect lipid plasma concentrations, interact with study medications, or that may affect clinical laboratory variables such as intermittent systemic steroids, isotretinoin, and immunosuppressive agents" were not allowed. Any drugs associated with

rhabdomyolysis when combined with HMGRIs, "such as cyclosporine and erythromycin," also were not allowed.

Patient Withdrawal from Study:
Patients were allowed to withdraw from study "at any time." Additionally, if at any time a pt:

- Became pregnant or began breast-feeding, she was withdrawn from study;
- Showed ALT or AST levels >3 times upper limit of normal (ULN) or had creatine phosphokinase (CPK) level >10 ULN, then repeat lab was performed within 4-10 days. If repeat test still exceeded the above guidelines, pt was withdrawn; or
- Experienced any intolerable adverse event(s), or "if continued participation jeopardized the patient's health," he/she was withdrawn from study.

3.3.2 Endpoints
Primary efficacy parameters were percentage change from baseline by end of each treatment period in measured values for LDL-C and IDL-C + VLDL-C.

Secondary efficacy parameters included percentage change from baseline by end of each treatment period in measurements for: TC, TG, VLDL-C, IDL-C, HDL-C, VLDL-C, VLDL-C/TG, apo B (total, VLDL, LDL), apo CIII, and apo E.

Tertiary efficacy parameters were assessment of:

1) triglyceride lipolysis in those pts who had TG <1000 mg/dL while on diet alone and who in addition agreed to participate in this evaluation. Effect on TG lipolysis was assessed by calculating change from baseline in area under the curve (AUC) for TG and for retinol palmitate as measured at the end of each treatment period; and
2) cholesterol homeostasis, which was assessed by change of mononuclear leukocytes counts as well as percentage change in mevalonic acid (which is the immediate product of HMG-CoA reductase) from baseline (week -2) to the end of each treatment period (weeks 8, 16, 24, and 32). "Single vertical spin ultracentrifugation changes from baseline graphs were determined" at the end of each treatment period.

3.3.3 Statistical Methods (in addition see statistician's review)
Primary analysis was performed on ITT patient sample comprising all patients randomized who had a baseline observation and at least 1 treatment observation available.

3.4 Results
3.4.1 Disposition/demographics
Sixteen pts participated, 10 men and 6 women. Ages ranged from 29 to 72. Fifteen of 16 were white. It is said that baseline demographics were similar among all treatment

sequence groups. Pt 4, who had been randomized initially to Treatment Sequence S/A80/G/A10, had his treatment medications inadvertently reversed during his third and fourth treatment periods. Therefore, third and fourth period efficacy data from this patient were excluded from all statistical analyses, although 1st and 2nd period data were included, and all data from all periods from this subject were considered for analysis of safety.

3.4.2 Efficacy

Dietary counseling continued throughout the entire treatment phase; dietary diaries, in addition, were completed at weeks 8, 16, 24, and 32. Based on the "investigator's opinion," all patients were compliant with respect to medication and diet throughout the study. No prohibited meds were used during the entire study. No patient withdrew during the trial.

The tables below are reproduced directly from the submission from the sponsor.

TABLE 6. Summary of the Primary, Secondary, and Tertiary Efficacy Parameters by Treatment
Mean (Standard Error)
(Page 1 of 3)

Parameter[a]	A10		A80		G		S	
Primary Efficacy Parameters								
IDL-C + VLDL-C								
N	15		16		15		16	
Baseline (mg/dL)	258	(35.8)	251	(34.3)	258	(35.8)	251	(34.3)
Final (mg/dL)	180	(31.3)	103	(16.6)	160	(27.4)	180	(27.6)
Adj % Change	-34	(4.8)	-58	(4.5)	-33	(4.8)	-28*	(4.5)
LDL-C								
N	15		16		15		16	
Baseline (mg/dL)	57	(8.4)	56	(8.0)	57	(8.4)	56	(8.0)
Final (mg/dL)	51	(4.9)	39	(5.0)	81	(8.3)	45	(3.4)
Adj % Change	20	(10.3)	-6	(9.8)	86	(10.3)	10	(9.8)
Secondary Efficacy Parameters								
TC								
N	15		16		15		16	
Baseline (mg/dL)	558	(83.6)	539	(80.5)	558	(83.6)	539	(80.5)
Final (mg/dL)	320	(46.6)	201	(19.7)	322	(42.3)	297	(35.0)
Adj % Change	-40	(3.3)	-57	(3.2)	-34	(3.3)	-41*	(3.2)
TG								
N	15		16		15		16	
Baseline (mg/dL)	1472	(492.9)	1403	(466.2)	1472	(492.9)	1403	(466.2)
Final (mg/dL)	695	(229.1)	380	(67.2)	420	(99.5)	593	(114.0)
Adj % Change	-40	(3.8)	-56	(3.6)	-52	(3.8)	-36*	(3.6)

TABLE 6. Summary of the Primary, Secondary, and Tertiary Efficacy Parameters by Treatment

Mean (Standard Error)

(Page 2 of 3)

Parameter[a]	A10		A80		G		S	
Secondary Efficacy Parameters (cont)								
VLDL-C								
N	15		16		15		16	
Baseline (mg/dL)	205	(31.2)	199	(29.8)	205	(31.2)	199	(29.8)
Final (mg/dL)	145	(28.1)	77	(12.2)	119	(23.7)	147	(25.0)
Adj % Change	-32	(5.4)	-59	(5.1)	-35	(5.4)	-26*	(5.1)
IDL-C								
N	15		16		15		16	
Baseline (mg/dL)	47	(3.8)	46	(3.7)	47	(3.8)	46	(3.7)
Final (mg/dL)	35	(5.0)	22	(3.2)	41	(5.9)	33	(4.1)
Adj % Change	-28	(4.6)	-50	(4.3)	-13	(4.6)	-27*	(4.3)
HDL-C								
N	15		16		15		16	
Baseline (mg/dL)	35	(2.9)	35	(2.7)	35	(2.9)	35	(2.7)
Final (mg/dL)	35	(3.4)	38	(2.9)	38	(2.5)	35	(3.2)
Adj % Change	3	(3.6)	13	(3.5)	11	(3.6)	1*	(3.5)
VLDL-C/TG ×10								
N	15		16		15		16	
Baseline	2	(0.2)	2	(0.2)	2	(0.2)	2	(0.2)
Final	3	(0.2)	2	(0.2)	3	(0.3)	3	(0.2)
Adj % Change	28	(8.7)	10	(8.2)	57	(8.7)	41*	(8.2)
Apo B (Total)								
N	15		16		14		16	
Baseline (mg/dL)	734	(177.8)	704	(169.1)	690	(184.9)	704	(169.1)
Final (mg/dL)	374	(112.1)	177	(26.6)	217	(23.7)	252	(33.5)
Adj % Change	-47	(3.7)	-66	(3.5)	-53	(3.9)	-52*	(3.5)
Apo B (VLDL)								
N	14		14		14		14	
Baseline (mg/dL)	74	(10.0)	74	(10.0)	74	(10.0)	74	(10.0)
Final (mg/dL)	104	(16.5)	73	(13.4)	91	(20.4)	142	(26.6)
Adj % Change	97	(20.7)	27	(20.7)	62	(20.7)	124*	(20.7)
Apo B (LDL)								
N	6		2		5		3	
Baseline (mg/dL)	636	(278.9)	713	(544.0)	881	(316.9)	876	(323.3)
Final (mg/dL)	403	(245.7)	171	(86.2)	125	(27.8)	234	(77.5)
Adj % Change	-46	(13.0)	-61	(18.9)	-77	(12.5)	-62	(17.0)

TABLE 6. Summary of the Primary, Secondary, and Tertiary Efficacy Parameters by Treatment

Mean (Standard Error)

(Page 2 of 3)

Parameter[a]	A10		A80		G		S	
Secondary Efficacy Parameters (cont)								
Apo C-III								
N	15		16		15		16	
Baseline (mg/dL)	30	(2.6)	29	(2.5)	30	(2.6)	29	(2.5)
Final (mg/dL)	25	(2.6)	21	(2.7)	24	(2.4)	25	(2.3)
Adj % Change	-16	(7.1)	-31	(6.7)	-12	(7.1)	-8*	(6.7)
Apo E								
N	15		16		15		16	
Baseline (mg/dL)	41	(3.4)	40	(3.4)	41	(3.4)	40	(3.4)
Final (mg/dL)	30	(3.4)	23	(2.7)	31	(3.0)	32	(3.7)
Adj % Change	-27	(4.7)	-41	(4.4)	-24	(4.7)	-20*	(4.4)
Tertiary Efficacy Parameters								
AUC in Retinol Palmitate								
N	4		5		4		5	
Baseline	175	(11.7)	159	(18.4)	175	(11.7)	159	(18.4)
Final	133	(6.9)	99	(19.8)	100	(12.7)	120	(15.7)
Adj Change	-28	(14.7)	-57	(11.1)	-61	(14.7)	-40	(11.1)
AUC in Triglycerides								
N	4		5		4		5	
Baseline	13082	(3377.6)	11726	(2946.8)	13082	(3377.6)	11726	(2946.8)
Final	9038	(2476.1)	6378	(1576.6)	5828	(793.1)	7923	(2102.8)
Adj Change	-2268	(965.9)	-4433	(728.8)	-5512	(965.9)	-3239	(728.8)
Mevalonic Acid								
N	8		7		9		9	
Baseline (μ/24 hr)	4	(0.6)	4	(0.3)	4	(0.5)	4	(0.5)
Final (μ/24 hr)	3	(0.5)	2	(0.2)	3	(0.5)	4	(0.7)
Adj % Change	-29	(15.3)	-63	(16.8)	-18	(13.3)	-22	(14.9)
Mononuclear Leukocytes								
N	11		13		11		13	
Baseline	7	(1.3)	7	(1.2)	7	(1.5)	7	(1.2)
Final	10	(1.3)	19	(2.3)	7	(1.7)	14	(1.7)
Adj Change	4	(1.6)	11	(1.4)	1	(1.6)	7*	(1.4)

A10 = Atorvastatin 10 mg QD; A80 = Atorvastatin 80 mg QD; G = Gemfibrozil 600 mg BID; S = Simvastatin 40 mg QD.

* Simvastatin 40 mg QD treatment significantly different from atorvastatin 80 mg QD treatment ($p < 0.05$).

[a] Adjusted means based on ANOVA model with effects due to sequence, patient within sequence, treatment, and period.

Treatment with atorvastatin 10 mg daily in this study population resulted in a "substantial adjusted mean decrease" of 34% in IDL-C + VLDL-C. In addition, it is said that TC, TG, VLDL-C, IDL-C, apo B, apo CIII, and apo E "were favorably decreased" from baseline levels.

Treatment with atorvastatin 80 mg daily resulted in "best overall response" among the 4 treatments employed. IDL-C + VLDL-C was reduced through this regimen by 58%; TC, TG, VLDL-C, IDL-C, apo B, apo CIII, and apo E were reduced to "a greater degree than any of the other treatment groups." In addition, LDL-C was reduced by 6% from baseline following this treatment.

Treatment with gemfibrozil 600 mg BID resulted in "substantial adjusted mean decrease in IDL-C + VLDL-C of 33%," in addition to "beneficial decreases in TC, TG, VLDL-C, IDL-C, apo B, apo CIII, and apo E." It is stated that most of these decreases were similar to those experienced when patients were given atorvastatin 10 mg QD. This regimen of this agent as utilized also resulted in an adjusted mean change from baseline of an increase in LDL-C of 86%.

Treatment with simvastatin 40 mg per day "had effects similar to" atorvastatin 10 mg daily; there was a 28% adjusted mean decrease in IDL-C + VLDL-C, and there were "favorable reductions" in TC, TG, VLDL-C, IDL-C, apo B, apo CIII, and apo E. Adjusted mean percentage change in LDL-C was similar for simvastatin 40 mg daily and atorvastatin 10 mg per day (10% vs 20%).

Triglyceride lipolysis: only 5 of the 16 pts in the entire group qualified and agreed to participate in evaluation of AUC for retinol palmitate and TG. Patients showed similar reduction in AUC for retinol palmitate and TG while on the regimen of gemfibrozil that was utilized as compared to atorvastatin 80 mg per day. It is said that these data "indicate better postprandial lipoprotein clearance induced by atorvastatin 80 mg QD than atorvastatin 10 mg QD or simvastatin" in the dosage and regimen employed for this trial.

Cholesterol homeostasis: production of mevalonic acid was reduced by an average of 63% from baseline when atorvastatin 80 mg per day was administered. The other 3 regimens all reduced mevalonic acid production but to a lesser degree; amounts of reduction were similar among the three: 29% by atorvastatin 10 mg daily, 18% by gemfibrozil 600 mg BID, 22% by simvastatin 40 mg daily. It is also said that the "adjusted change of circulating mononuclear leukocytes was significantly greater for patients while on atorvastatin 80 mg QD than simvastatin."

4 Safety Review

4.1 Exposure

All patients were exposed to the same drugs and same dosage regimen for each patient and for the same durations, although, as described, in differing sequence.

4.2 Demographics

Of the total group, 10 were men and 6 were women. Two were older than 70 years.

4.3 Disposition

All subjects completed their 8-week trial on each drug.

4.4 Adverse Events

4.4.1 Clinical Events

During Period 1, 7 patients experienced 8 adverse events:

a) atorvastatin 10 mg QD: 2; nausea/vomiting, bronchitis
b) atorvastatin 80 mg QD: 3; flatulence, anxiety, sty
c) gemfibrozil: 1; hypoglycemia
d) simvastatin: 1; constipation and dyspepsia

The only adverse event during Period 1 that was felt to be associated with treatment was constipation by one subject while on simvastatin.

Overall during the entire study, 15 of 16 subjects experienced at least one adverse event. These events were similar across treatments and "not unexpected for this population of patients." During All Periods, adverse events of the 4 treatments were related most often to the body as a whole and to the digestive system. Numbers of patients reporting any adverse event were similar among the 4 treatments; 7 patients reported adverse events on atorvastatin 10 mg daily, 13 patients while on atorvastatin 80 mg per day reported adverse events, 9 patients when on gemfibrozil 600 mg BID reported adverse happenings, and 15 when given simvastatin experienced adverse occurrences.

However, patients reporting adverse events that were actually attributed to the treatments were few in number, and those numbers were "similar between treatment groups," with none on atorvastatin 10 mg reporting adverse effects, 2 on atorvastatin 80 mg/day reporting adverse happenings, 1 patient on gemfibrozil experiencing attributed adverse finding, and 5 patients on simvastatin reporting attributed adverse events. Adverse events associated with atorvastatin 80 mg daily were asthenia/malaise and dyspepsia, the single event associated with gemfibrozil was diarrhea, and events associated with simvastatin were asthenia in 2 patients, constipation, diarrhea, and increased cough.

All adverse events from all treatments used were mild in intensity, except for 1 serious event (chest pain) considered severe while patient was on simvastatin; this event was not associated with drug.

There were no deaths or withdrawals due to adverse events during this entire trial.

4.4.2 Clinical labs

Those laboratory measurements that were actually performed allowed "only for determination of the amount of change in each treatment sequence group from baseline to final value." Thus, these tests "did not allow for any comparison between treatments."

The median change from baseline to final value was determined for patients who had both of these values as well as for treatment sequence group. It is said that during Period 1 the number of patients with any reported abnormal lab value was similar among the 4 regimens: 2 on atorvastatin 10 mg daily, 2 on atorvastatin 80 mg per day, 3 on gemfibrozil, and 3 on simvastatin. During All Periods, the number of patients with any abnormal lab value, it is said, was also similar: 6 on atorvastatin 10 mg, 10 on atorvastatin 80 mg, 8 on gemfibrozil, and 7 on simvastatin. The "majority of these abnormalities were minor elevations of ALT or AST, none of which were considered to be clinically important."

4.5 Conclusions regarding safety

There were no unusual adverse events or clinical lab abnormalities observed in the trial presented here in which atorvastatin was administered for this limited duration. This trial has been completed; no safety update is necessary. There has been a sufficiently longer duration of drug intake when drug has been administered for its presently approved indication(s) so that we may feel fairly confident that no novel or unexpected adverse effects would become evident in clinical use for treatment of type III hyperlipoproteinemia.

5 Labeling in toto (and by section if relevant)

Changes and/or proposed revisions in labeling are actually fairly few and limited in scope, number, and locations. A sentence has been added to Clinical Pharmacology to describe the effect of drug in dysbetalipoproteinemia. Clinical Studies has an additional sentence to cite the amounts of reduction in parameters in Type III and to ~~list~~ the specific factors that are reduced in serum. A sentence is appended to Indications to add the new recommended treatment category. The sentence to describe dosage range to be employed in type III hyperlipoproteinemia has been placed under Dosage and Administration.

6 Conclusions

The data presented in this supplemental NDA appear to support both the efficacy and safety of atorvastatin when administered in dosage up to 80 mg daily and when used for the treatment of dysbetalipoproteinemia (Fredrickson type III hyperlipoproteinemia) in adults. The drug appears to be fairly well tolerated in patients who were exposed for up to 8 weeks in this trial, which was conducted to gain experience in this relatively uncommon condition.

Furthermore, the drug is already approved and on the market for other indications, and total experience in the other condition(s) also adds to entire safety profile and background of the agent. The frequency and type of adverse events that occurred when this agent was

administered were not different than in patients given 2 other drugs received by the same patient group. There are no novel safety issues that appear evident or arise from all the data and experience collected from this investigation and presented in this application.

The labeling has been altered relatively little at this time; changes made have been merely to add this indication, to add the changes in those parameters which are effected by the drug, and to give the dosage and regimen to be recommended for this indication. The labeling appears adequate for proper and safe use of the product in the subject disorder and in the patient population studied, and I have no further changes or recommendations for the package insert.

7 Recommendations

1. This supplement, especially Appendix D.1 which begins on pg 352 ff of Vol 1, should be reviewed and evaluated by FDA statistician to evaluate if there are any problems with or disagreement with the ANOVA model of statistical analysis employed by the company.
2. Unless the statistician finds difficulties with statistical results and/or statistical conclusions reached by the sponsor, this supplemental NDA may be approved without any further modifications, requests, or additional actions.

/S/

Elton Herman

See team leader note
for review and
labeling recommendations.
Stat review not needed.

/S/
6-23-98

cc: NDA 20-702 supplement 005
HFD-510
HFD-510/EHerman/06-15-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020702/S003 and 020702/S005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

SIMONEAU

Clinical Pharmacology & Biopharmaceutics Review FEB 9 1998

NDA:	**20-702**
SUBMISSION DATE:	**July 16, 1997** **July 22, 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:	**Efficacy Supplement S-005**

SYNOPSIS:

This submission is an efficacy supplement for the treatment of patients with Fredrickson Types III, IV and V hyperlipoproteinemia and concerns User Fee payment.

There are no PK issues.

/S/

2/6/98
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II

RD/FT initialed by Hae Young Ahn, Ph.D., Team leader_ /S/ 2/9/98

cc: NDA 20-702, HFD-510, HFD-870 (Jones), CDR (Murphy).

CODE: NC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020702/S003 and 020702/S005

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

ITEM 13.
PATENT AND MARKET EXCLUSIVITY INFORMATION

13.1. Patent Information

NDA Number:	20-702
Applicant:	Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company PO Box 1047 Ann Arbor, MI 48106
Active Ingredient:	Atorvastatin calcium is [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ and its molecular weight is 1209.42.
Medical Use:	Atorvastatin is a synthetic lipid-lowering agent.
Strength:	10, 20, and 40 mg
Dosage Form:	Tablet
Trade Name:	Lipitor™
Generic Name:	Atorvastatin (calcium)
Patent Statement:	Three patents cover atorvastatin (calcium)

Atorvastatin Calcium
Tablets

U.S. Patent No.:	4,681,893
Expiration Date:	May 30, 2006
Patent Type:	Compound per se formulation method of use
Assignee:	Warner-Lambert Company

U.S. Patent No.:	5,273,995
Expiration Date:	December 28, 2010
Patent Type:	Compound per se formulation method of use

U.S. Patent No.:	5,385,929
Expiration Date:	May 4, 2014
Patent Type:	Compound per se formulation method of use

The undersigned declares that Patent Nos. 4,681,893, 5,273,995 and 5,385,929 cover a formulation and method of use of atorvastatin, which product is the subject of this application for which approval is sought.

Charles W. Ashbrook

CA1P4023.96

ITEM 13.
Request for Market Exclusivity

As provided for by 21 CFR 314.108(b)(4), Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, is requesting a 3-year period of market exclusivity for Lipitor® for the treatment of Fredrickson Type III dyslipidemia. Parke-Davis certifies that the active moiety, atorvastatin calcium, meets the criteria for the exclusivity period specified in 21 CFR 314.50(j)(4) and in 21 USC 355(j)(4)(D)(iii) and 355(c)(3)(D)(iii), specifically:

1. No drug product containing atorvastatin calcium for the treatment of Fredrickson Type III dyslipidemia, for which approval is sought in this application, has been previously approved.

2. Three new clinical investigations, other than bioavailability or bioequivalence studies, are being submitted to support this application. Parke-Davis certifies that these clinical studies have not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved NDA.

3. a. Parke-Davis certifies that the company has thoroughly searched the scientific literature and, to the best of our knowledge, no published studies or publicly available reports of clinical investigations with atorvastatin calcium in the treatment of Fredrickson Type III dyslipidemia are relevant to support the application.

   b. Parke-Davis certifies that, in the applicant's opinion, the present application could not be approved without the new clinical investigations.

4. Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, is the sponsor named in the Form FDA 1571 for under which the clinical investigations identified in Item 2 above were conducted.

EXCLUSIVITY SUMMARY for NDA # 20-702 SUPPL # S-003 and S-005

Trade Name Lipitor **Generic Name** Atorvastatin
Applicant Name Parke Davis **HFD-** 510

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /__/ NO /✓/

   b) Is it an effectiveness supplement?

   YES /✓/ NO /__/

   If yes, what type? (SE1, SE2, etc.) SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.:

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 yrs eff 314.108 (b)(4) -- APPEARS THIS WAY ON ORIGINAL

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

APPEARS THIS WAY ON ORIGINAL

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

APPEARS THIS WAY ON ORIGINAL

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-702 Lipitor

NDA # _____ _____

NDA # _____ _____

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /__/ APPEARS THIS WAY ON ORIGINAL

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /__/

APPEARS THIS WAY
ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 981-039

Investigation #2, Study # 981-038, 042, 055

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /__/	NO /✓/
Investigation #2	YES /__/	NO /✓/
Investigation #3	YES /__/	NO /__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /__/	NO /✓/
Investigation #2	YES /__/	NO /✓/
Investigation #3	YES /__/	NO /__/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 981-055

Investigation #2, Study # 981-038, 042, 055

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES / ✓ / NO / ___ / Explain: ____

_____

Investigation #2

IND # ____ YES / ✓ / NO / ___ / Explain: ____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / ___ / Explain _____ NO / ___ / Explain _____

_____ _____

_____ _____

APPEARS THIS WAY
ON ORIGINAL

Investigation #2 ! !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/ 7/6/98

Signature Date

Title: Project Manager

/S/ 7/9/98

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

DA/BLA # 20-702 Supplement # S-003 S-005 Circle one (SE1) SE2 SE3 SE4 SE5 SE6

HF S10 Trade and generic names/dosage form: Lipitor (atorvastatin) Action: (AP) AE NA

APPEARS THIS WAY ON ORIGINAL

Applicant Parke Davis Therapeutic Class Lipid Altering Agents

Indication(s) previously approved to reduce total-C, LDL-C, apoB, and TG levels in pts w Primary hyper + Mixed dys lipidemia

Pediatric information in labeling of approved indication(s) is adequate __ inadequate __

Proposed indication in this application S-003 add treatment of FREDERICKSON Types IV + V

S-005 add treatment of FREDERICKSON Type III

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? __Yes (Continue with questions) ✓No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

APPEARS THIS WAY ON ORIGINAL

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- __ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- __ c. The applicant has committed to doing such studies as will be required.
  - __ (1) Studies are ongoing,
  - __ (2) Protocols were submitted and approved.
  - __ (3) Protocols were submitted and are under review.
  - __ (4) If no protocol has been submitted, attach memo describing status of discussions.
- __ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? __Yes ✓No

APPEARS THIS WAY ON ORIGINAL

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Team leader (e.g., medical review, medical officer, team leader)

/S/ /medical team leader 7-8-98

Signature of Preparer and Title Date

Orig NDA/BLA #_____

HF_____/Div File

NDA/BLA Action Package

HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

ITEM 16.
Certification of Generic Drug Enforcement Act of 1992

Warner-Lambert Company certifies that it is not debarred, and to the best of its knowledge Warner-Lambert Company did not and will not use in any capacity the services of any person debarred under Section 306(a) or 306(b) of the Federal Food, Drug, and Cosmetic Act in connection with this application.

APPEARS THIS WAY
ON ORIGINAL

Pharmaceutical Research
2800 Plymouth Road
Ann Arbor, MI 48105
Phone: 313-996-7590
Facsimile: 313-996-7895

ORIGINAL

NDA SUPPL AMENDMEN

PARKE-DAVIS
People Who Care

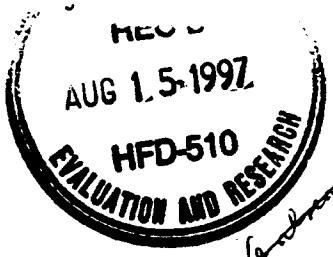
Sean Brennan, Ph.D.
Senior Director
Worldwide Regulatory Affairs

August 14, 1997

NDA 20-702
Ref. No. 44
Lipitor® (atorvastatin calcium) Tablets

Re: Amendment to Efficacy Supplements (S-003 and S-005); Environmental Assessment

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
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) Tablets and to the Efficacy Supplements (S-003 and S-005) submitted on July 16, 1996, for the treatment of patients with Fredrickson Types III, IV and V hyperlipoproteinemia. Reference is also made to two separate telephone conversations with Dr. Xavier Ysern of your division: one with Dr. Margaret Uprichard of Parke-Davis on August 5, 1997, and the other with Dr. Philip Simonson of Parke-Davis on August 12, 1997.

In both telephone conversations, Dr. Ysern stated that a request for a waiver of the Environmental Assessment requirements would be needed for the additional indications. The addition of these indications do not significantly increase the marketing forecasts for Lipitor. Therefore, the Environmental Assessment information previously submitted and approved is not effected. For complete copies of the Confidential and Freedom of Information Environmental Assessment reports, please refer to the NDA Amendments submitted on October 25, 1996, (reference numbers 18 and 19 respectively).

noted
9/5/97

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\081397-44

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

June 23, 1998

NDA 20-702/S-003 and S-005
Ref. No. 68
Lipitor® (atorvastatin calcium) Tablets

Re: FDA Request for Information

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

Dear Dr. Sobel:

Reference is made to our Supplements 003 (Fredrickson Type III dyslipidemic patients) and 005 (Fredrickson IV and V dyslipidemic patients) to NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets and Ms. Margaret Simineau's June 15 request for Patent Information and debarment certification for each supplement.

Enclosed for each supplement are items 13 and 16, the Patent and debarment certification statements as requested.

Should you have any questions regarding this submission, please contact me at 734/622-7425 or FAX 734/622-3283.

Sincerely,

Byron Scott

Byron Scott, R. Ph.
Director
Worldwide Regulatory Affairs

BS\rm
T:\nda\20-702\062398-68

Attachments

Desk Copy: Ms. Margaret Simoneau (HFD-510)

Pharmaceutical Research
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (734) 622-7000

PARKE-DAVIS

June 2 1998

NDA 20-702/S-005
Ref. No. 65
Lipitor® (atorvastatin calcium) Tablets

Re: Response to Question

DESK COPY

Solomon Sobel, M.D.
Director
Division of Metabolic 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

Dear Dr. Sobel:

Reference is made to our pending Supplement 005 to NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets and Dr. Shen's telephone call on May 26, 1998. In accordance with Dr. Shen's request, enclosed is a floppy disk containing a Microsoft Word 6.0 (Office 95) version of the file for 981-38, Research Report 720-03335 entitled, "A 4-Week, Dougle-Blind, Placebo-Controlled, Multicenter Study of Once Daily Atorvastatin (CI-981) in Patients with Elevated Triglycerides (Protocol 981-38)."

The file has been scanned with McAfee VirusScan version 3.0.2.

Should you have any questions regarding this submission, please contact me at 7343622-7425 or FAX 734/622-3283.

Sincerely,

Byron Scott

Byron Scott, R. Ph.
Director
Worldwide Regulatory Affairs

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Enclosure

Desk Copy: Dr. Shen

NDA SUPPLEMENT ORIGINAL

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

PARKE-DAVIS
People Who Care

NDA NO. [illegible] REF. NO. [illegible]
NDA SUPPL FOR [illegible]

July 22, 1997

NDA 20-702
Ref. No. 42
Lipitor® (atorvastatin calcium) Tablets

Re: Efficacy Supplement S-005

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 23 1997
HFD-510

Dear Dr. Sobel:

Reference is made to our approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets, to our supplemental NDA for the treatment of patients with Fredrickson Types III, IV, and V hyperlipoproteinemia submitted July 16, 1997 (Ref. No. 40), and to today's telephone conversation with Ms. Enid Galliers and Dr. David Orloff of your Division. During our telephone conversation we were informed that Fredrickson Types IV and V and Fredrickson Type III represent two distinct indications

The indication for patients with Fredrickson Types IV and V was assigned supplement number S-003 and is covered by the initial payment of sent to the FDA on June 24, 1997. A second initial payment of for the indication in patients with Fredrickson Type III (supplement number S-005) was transferred electronically to the

We understand the review clock for this indication will begin today. We apologize for the confusion and any inconvenience caused by this oversight and appreciate the Division bringing it to our attention.

Noted. No new CMC issues. approvable from the chemist viewpoint /S/

/S/ 9/4/97

NO PK issues /S/

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: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Sincerely,

Margaret J. Uprichard

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

MU\rm
t:\nda\20-702\072297-42

Attachment

/S/
8-1-97

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

NDA SUPPLEMENT ORIGINAL

PARKE-DAVIS
People Who Care

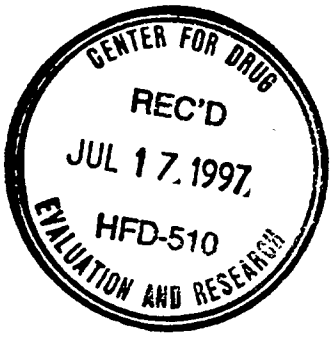
July 16, 1997 NDA NO. [redacted] REF. NO. 2003

NDA SUPPL FOR [redacted]

NDA 20-702
Ref. No. 40 for Fredrickson Types IV & V only
Lipitor® (atorvastatin calcium) Tablets

Re: Efficacy 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 our approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets and to our May 16, 1997, meeting with your Division during which we discussed a supplemental NDA for the treatment of patients with Fredrickson Types III, IV, and V hyperlipoproteinemia. Meeting minutes are found behind Tab A. We are now submitting this SNDA to support an indication for Lipitor as adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (*Fredrickson* Types IV and V) who present a risk for pancreatitis and for patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) that do not respond adequately to diet.

E this indication is supplement 005

Primary dysbetalipoproteinemia (*Fredrickson* Type III) is an extremely rare disorder affecting less than one in 10,000 patients in the United States. Patients with isolated hypertriglyceridemia (*Fredrickson* Types IV and V) are at risk for pancreatitis. Niacin and fibrates are typically used to treat hypertriglyceridemia in these patients; however, therapeutic response is often unsatisfactory and may be complicated by unpleasant side effects or a paradoxical increase in low-density lipoprotein cholesterol (LDL-C). Historically, TG lowering > 30% has been demonstrated by drugs approved for isolated hypertriglyceridemia. Treatment of these patients with atorvastatin results in mean reductions in total TG ≥ 30%. Atorvastatin is well-tolerated and does not cause the unwanted increase in LDL-C as some existing therapies.

As required by the Prescription Drug User Fee Act of 1992, a check for as our initial payment for this supplement was sent to the FDA on June 24, 1997. A User Fee Cover Sheet, Form FDA 3397, is found in Item 18.

NDA NO. [illegible] REF. NO. _____

NDA SUPPL FOR SC 1

ORIGINAL

In accordance with 21 CFR §314.70, we are submitting the following documents in support of this indication:

- Application Form (356H)
- Item 1 Index to the SNDA
- Item 2 Draft Labeling - annotated (four copies)

- Item 8 Clinical Data

  Four clinical study reports are intended to support this indication; three of the study reports (Studies 981-38, -42, and -55) were submitted in the initial NDA and their location within the NDA is referenced in Item 8 of this submission. The fourth report (Study 981-39) is included with this submission.

In addition to the paper copy submission, the clinical documents and data for the three NDA study reports can be accessed through the network Parke-Davis electronic regulatory submission (ERS). The reports are listed in the existing ERS Table of Contents under "Section 8.8, Clinical References" as number 18 (981-38), number 14 (981-42), and number 15 (981-55). The data and study report for Study 981-39 have been integrated into the existing Oracle database and are accessible through the ERS. In accordance with the waiver granted by Dr. Woodcock for the initial NDA, the paper version of Case Report Forms (CRFs) and CRF tabulations have been omitted from this efficacy supplement. CRFs for all patients in all four studies may be accessed through the ERS.

The data for Study 981-39 are also being submitted on an IBM Compatible 3.5" DS, HD, 1.44 MB diskette containing two SAS databases in SAS Transport format. The file ***D981039.trn*** contains all of the raw data for Study 981-39. The file ***D981039E.trn*** contains the derived efficacy data. The transport files can be copied to the reviewer's own SAS library with the following statements:

libname xxxx 'SAS library name';
libname yyyy xport 'D981039.trn';
proc copy in=yyyy out=xxxx;
(repeat for efficacy data)

The diskette has been scanned for all known computer viruses using McAfee VirusScan NT, version 2.5.3a. Hardcopy PROC CONTENTS for the SAS databases are found behind Tab B.

For questions regarding this submission during the review, please contact me at 313/996-4906 or FAX 313/998-3283 or e-mail at uprichm@aa.wl.com. Technical questions on the ERS may be directed to me or to Mr. William Rosen of Parke-Davis' systems development group at 313/996-5168 or e-mail at rosenw@aa.wl.com.

Sincerely,

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

MU\rm
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Attachments

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE