

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number: 020702/S003 and 020702/S005**

**Trade Name: LIPITOR TABLETS**

**Generic Name: ATORVASTATIN CALCIUM**

**Sponsor: PARKE-DAVIS PHARMACEUTICAL RESEARCH**

**Approval Date: 07/10/98**

**Indication(s): AS AN ADJUNCTIVE THERAPY TO DIET FOR THE TREATMENT OF PATIENTS WITH ELEVATED SERUM TRIGLYCERIDE LEVELS AND BY PATIENTS WITH PRIMARY DYSBETALIPOPROTEINEMIA WHO DO NOT RESPOND ADEQUATELY TO DIET.**

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION: 020702/S003 and 020702/S005**

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter				X
Final Printed Labeling		X		
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	X			
Biopharmaceutics Review(s)				
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number: 020702/S003 and 020702/S005**

**APPROVAL LETTER**



NDA 20-702/S-003  
NDA 20-702/S-005

JUL 10 1998

Parke-Davis Pharmaceutical Research, agent for  
Warner-Lambert Export, Limited  
Attention: Byron Scott, R.Ph.  
Director Worldwide Regulatory Affairs  
2800 Plymouth Road  
Ann Arbor, MI 48105

**BEST POSSIBLE COPY**

Dear Mr. Scott:

Please refer to your supplemental new drug applications S-003 dated July 16, 1997, received July 17, 1997, and for supplement S-005 dated July 22, 1997, received July 23, 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 for Supplement-003 dated August 14, 1997, June 23, 25 (2), 30, and July 8, 1998. The user fee goal date for this application is July 17, 1998. For Supplement-005 we acknowledge receipt of your submissions dated August 14, 1997, April 27, June 2, 15, 23, 25(2), 30, and July 8, 1998. The user fee goal date for this application is July 23, 1998.

The supplemental new drug application S-003 provides for the use of Lipitor (atorvastatin calcium) Tablets as an adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (Frederickson Type IV.)

The supplemental new drug application S-005 provides for the use of Lipitor by patients with primary dysbetalipoproteinemia (Frederickson Type III) who do not respond adequately to diet.

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

The final printed labeling (FPL) must be identical to the draft labeling submitted on July 8, 1998. Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

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, these submissions should be designated "FPL for approved NDA 20-702/S-003 and S-005." Approval of these submissions by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

If a letter communicating important information about this drug product (i.e., a "Dear Healthcare Practitioner" letter) is 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 20857

**BEST POSSIBLE COPY**

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely,

*Solomon Sobel, M.D.*

Director

Division of Metabolic and Endocrine Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020702/S003 and 020702/S005**

**MEDICAL REVIEW(S)**

NDA 20-702/S-003/S-005  
Lipitor (atorvastatin calcium) tablets  
Parke-Davis

Memo to the file: 7-8-98

This supplement contains no safety updates, as all the trials were completed, without extensions, before the original submission.

In addition, the integrated summaries of safety and effectiveness are included in the medical reviews (medical officer and/or team leader).

Finally, no DSI inspection is required.

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

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ON ORIGINAL

/S/

7-8-98

APPEARS THIS WAY  
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7-9-98

*Dr. Orloff's memo  
will be covered  
in approval letter*

/S/

7-9-98

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NDA 20-702/S-003

LIPITOR (atorvastatin calcium)

Parke-Davis, Ann Arbor

Category: Lipid altering/HMG-CoA reductase inhibitor

Indication: treatment of patients with isolated hypertriglyceridemia at risk for pancreatitis

**Medical Team Leader review**

**Introduction**

Isolated hypertriglyceridemia due to elevations in VLDL, IDL, and remnant lipoproteins (Type IV) and accompanied by low HDL-C and small, dense LDL particles is associated with increased risk for atherosclerosis. Marked hypertriglyceridemia is further associated with a risk of pancreatitis. Elevation in triglycerides to these levels is, virtually by definition, indicative of the presence of chylomicrons (Type V). Patients will often see-saw between the these two phenotypes with chylomicronemia precipitated commonly by dietary indiscretion and alcohol use.

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In the past, the epidemiologic association between elevated TG levels and risk for CHD has been a point of argument, as it holds most consistently only in univariate analyses. This is because of the close correlation between elevated TG levels and low HDL-C, itself a strong predictor of heart disease risk. Furthermore, elevated plasma TG are often found in association with non-lipid metabolic risk factors for coronary heart disease. In addition, prospective studies specifically examining the impact on CHD risk of TG lowering in patients with Type IV are lacking. This is not to say there are no suggestive interventional data. In the Helsinki Heart Study, for example, the overall trial outcome was driven by the results in patients with the triad of moderately elevated LDL-C, elevated TG, and low HDL-C. Despite this and other suggestive evidence, labeling regarding efficacy in TG lowering in patients with Type IV has avoided the issue of impact on CHD risk. That is, drugs effective in lowering TG levels (e.g., niacin, fibrates) have been labeled for patients with hypertriglyceridemia at risk for pancreatitis.

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It is important to point out that despite the implication of such labeling, studies assessing effects of these agents on pancreatitis risk have neither been required by the Division nor are otherwise forthcoming from clinical investigators. In fact, most of the patients in pivotal proof-of-efficacy trials for TG-lowering drugs have had TG levels below 1500 mg/dL. Indeed, by the very nature of the patient population with elevated TG, both niacin and fibrates are most frequently used and are most effective in patients with Type IV HLP not obviously at risk for pancreatitis. In fact, drug therapy is usually ineffective in patients with Type V hyperlipoproteinemia. Thus, irrespective of labeling, with regard to the rationale for treatment in these patients, the circle is closed by the concept that lowering levels of TG-rich lipoproteins in many patients with Type IV HLP is of benefit in that it likely reduces CHD risk.

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The current supplement proposes a new indication for the use of atorvastatin in patients with Type IV HLP at risk for pancreatitis. The assessment of the appropriateness of such labeling depends on the strength of the lipid altering data and not on any evidence of reduction in the risk of pancreatitis. Again, the true rationale for treating such patients is to reduce heart disease risk. The database in support of this indication is quite small. All told, it includes 65 patients with isolated hypertriglyceridemia treated with atorvastatin as part of the original NDA. The acceptability of this relatively small exposure in support of a new indication is based on several factors. First of all, the safety profile of atorvastatin across the dosage range has been established on the basis of a ~2500-patient controlled clinical trial experience. Second, there appears to be no difference in the tolerability of the drug in patients with hypercholesterolemia, mixed dyslipidemia, or isolated hypertriglyceridemia. Finally, the efficacy with regard to lipid altering is clearly demonstrated in this small cohort of patients, with an understanding that summary statistics of central tendency may not fully describe the expected response to therapy. Because of small numbers of patients as well as variability in response to drug in patients with elevated TG, the data may well need to be described in more detail in labeling.

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Review of the lipid altering data in the patients with Type IV, particularly with regard to the changes in non-HDL-C, an indicator of atherogenic particle burden in patients with mixed dyslipidemia, suggest that

atorvastatin, and likely other statins, are useful adjuncts to diet in these patients, not to reduce the risk of pancreatitis but to lower the atherogenicity of plasma. As such, the indication for use of this and other statins should dispense with the reference to pancreatitis risk. To the extent that definitive interventional trials have not been conducted, however, a statement to the effect that the independent effect of TG lowering on CV morbidity and mortality has not been determined should be included in labeling and should accompany any promotion of this and other drugs for the treatment of these patients.

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**Methods**

For the current application, the sponsor has culled patient data from a number of different trials submitted to the original NDA. Two datasets were derived. The first included all patients from three studies (one placebo-controlled, dose-response study and two active-comparator-controlled studies) designed to assess the effect of atorvastatin in patients with normal LDL-C levels (< 160 mg/dL) and TG

The second dataset includes all patients from the NDA database with normal LDL-C (< 160 mg/dL) and TG > 500 mg/dL and shares some patients in common with the first dataset. All the studies included a diet lead-in period. Lipid inclusion criteria differed with regard to cutoff TG level, and in one study (981-038), the randomization was stratified by baseline LDL-C at a cutoff of 160 mg/dL. Other inclusion and exclusion criteria were constant across studies. The duration of treatment did vary, with lipid measurements made after 4 to 52 weeks of therapy, with a median of \_\_\_\_.

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The approach that examines patient responses across studies in the subgroup of patients with normal LDL-C and elevated TG is acceptable. Across the three small trials in hypertriglyceridemic patients, the effects of atorvastatin on TG levels in the subgroups with Type IV were significantly different from baseline (and in one trial from the concurrently treated placebo group) and comparable to or exceeding those of the active comparators (2 trials). These data are summarized in the original review of the atorvastatin NDA, in section 7.3. The pooling of the data from these trials is thus acceptable, and the additional patient data culled from the rest of the NDA database simply permits more thorough characterization of the response to atorvastatin across the dosage range in these patients.

The following table is reproduced, in part, from the current submission, and shows the numbers of patients in each data set by treatment.

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Table 1. Sponsor's datasets 2 and 3: Patients with isolated hypertriglyceridemia from NDA 20-702

Study	Plac	Atorva 10 mg	Atorva 20 mg	Atorva 80 mg	total Atorva
<b>Patients with isolated hypertriglyceridemia</b>					
981-038	12		13	11	24
981-042		10			10
981-055		6			6
subtotal	12	16	13	11	40
<b>Patients with TG &gt; 500 mg/dL</b>					
981-008		1			1
981-037		1			1
981-038	9		9	8	17
981-042		11			11
981-047		3			3
981-048				3	3
981-055		10			10
981-057		2			2
subtotal	9	28	9	11	48

total*	12	38	13	14	65
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\*Patients included in both datasets are counted only once in the bottom line total.

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### Results

The following tables summarize the response to treatment for the total cohort of placebo and atorvastatin-treated patients above. The changes from baseline are expressed as means with standard errors in the first table and as medians, with minimum and maximum values in the second table.

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Table 2. Combined patients with isolated elevated TG: Mean (SE) percent changes from baseline with p-values\*

Parameter	Placebo (N=12)	Atorva 10 mg (N=37)	Atorva 20 mg (N=13)	Atorva 80 mg (N=14)	Linear trend test**
Triglycerides	-3.3 (8.7) p=0.71	-35.7 (4.1) p<0.01	-32.4 (7.0) p<0.01	-45.1 (8.0) p<0.01	p=0.27
Total chol	0.2 (3.3) p=0.95	-27.1 (1.6) p<0.01	-32.9 (3.1) p<0.01	-42.6 (3.9) p<0.01	p<0.01
LDL-C	0.8 (5.2) p=0.88	-24.8 (2.4) p<0.01	-31.4 (4.2) p<0.01	-38.7 (3.9) p<0.01	p<0.01
HDL-C	2.2 (2.7) p=.43	12.8 (2.3) p<0.01	10.7 (2.5) p=0.01	9.9 (3.7) p<0.02	p=0.47
VLDL-C***	-0.7 (6.8) p=0.92	-43.1 (4.7) p<0.01	-45.3 (4.5) p<0.01	-54.9 (8.0) p<0.01	p=0.16
non-HDL-C	0.0 (3.8) p=0.99	-32.4 (1.8) p<0.01	-38.6 (3.3) p<0.01	-49.6 (4.4) p<0.01	p<0.01

\*p-value is from one-sample t test to determine if the percent change is significantly different from zero.

\*\* Linear trend test is based on a linear contrast of the three doses of atorvastatin using an analysis of variance model with the effect due to treatment.

\*\*\*N=35 for atorvastatin 10 mg

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ON ORIGINAL

Table 3. Combined patients with isolated elevated TG: Median (min, max) percent change from baseline with p-values\*

Parameter	Placebo (N=12)	Atorva 10 mg (N=37)	Atorva 20 mg (N=13)	Atorva 80 mg (N=14)
Triglycerides	-12.4 p=0.13	-41.0 p<0.01	-38.7 p<0.01	-51.8 p<0.01
Total chol	-2.3 p=0.79	-28.2 p<0.01	-34.9 p<0.01	-44.4 p<0.01
LDL-C	3.6 p=0.73	-26.5 p<0.01	-30.4 p<0.01	-40.5 p<0.01
HDL-C	3.8 p=0.38	13.8 p<0.01	11.0 p<0.01	7.5 p=0.04
VLDL-C**	-1.0 p=0.73	-48.8 p<0.01	-44.6 p<0.01	-62.0 p<0.01
non-HDL-C	-2.8 p=0.79	-33.0 p<0.01	-42.7 p<0.01	-51.5 p<0.01

\* p-value is from signed rank test to determine if the percent change is significantly different from zero

\*\* N=35 for atorvastatin 10 mg

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In this patient population, the response to atorvastatin with regard to lowering of total TG and VLDL-C is highly variable. As is clear from the medians and ranges of responses from baseline, the majority of

patients have some decrease in these lipid parameters from baseline. The comparison to placebo for the purposes of statistical testing is not valid, as the 12 placebo patients were all from one study. Nevertheless, for all doses, the mean and median changes from baseline are significantly different from zero. As expected in patients with dyslipidemias, this is not the case for the placebo group.

The responses with regard to TG and non-HDL-C lowering for the patient subgroup with baseline TG > 500 mg/dL were similar to those for the total cohort. The majority of the patients were in the former group. Among the 3 patients with baseline TG level > 1000 mg/dL, the responses to atorvastatin were similar to those among the patients with baseline TG < 1000 mg/dL. Only one patient had documented fasting chylomicrons in this series. Thus, the efficacy of atorvastatin has not been studied in patients with Type V hyperlipoproteinemia.

Among the 11 patients with baseline LDL-C > 160 mg/dL (mean 191 mg/dL), the response with regard to TG and non-HDL-C lowering were similar to those for the total cohort (N=64).

There was no meaningful correlation between the TG lowering response to treatment with atorvastatin and baseline TG level.

Finally, the trends in changes in TG, HDL-C and VLDL-C across atorvastatin doses were not significant. By contrast, the trend in non-HDL-C lowering was statistically significant.

#### Safety

There are no new safety issues arising in this subgroup of patients. Recall, all these patients were treated as part of the original NDA studies.

#### Discussion and Conclusions

In patients with hypertriglyceridemia, dysbetalipoproteinemia, and mixed dyslipidemia, lowering of total TG, VLDL-C, IDL-C are taken as evidence of benefit of treatment. Because of the tendency of some drugs, notably fibrates and niacin to increase LDL-C levels in patients with elevated TG-rich lipoproteins, however, it is often more telling to examine the effect of therapy on non-HDL-C, derived simply by subtracting the HDL-C level from the total-C level. Changes in non-HDL-C will roughly parallel those for TG, VLDL-C, and IDL-C as increases in LDL-C are usually only modest in absolute magnitude. Indeed, in patients with Type IV, even marked percentage increases in LDL-C are small, in absolute terms, because of low baseline LDL-C levels.

The results for changes in non-HDL-C in the patients with Type IV show that although variable, all patients showed a reduction with atorvastatin treatment. The trend test for the means across the three atorvastatin doses suggests a true dose-response. These data are further supportive of a role for atorvastatin, and likely other members of this class, in the primary therapy of some patients with isolated hypertriglyceridemia. A trial of statin therapy in these patients is justified on the basis of the current data.

#### Labeling

##### Clinical Pharmacology/Mechanism of Action

(the following replaces the last paragraph)

Lipitor reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Lipitor also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Lipitor reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Lipitor reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma triglycerides (TG) are frequently found in a triad with low

HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, in multivariate analyses, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. The effect of Lipitor on cardiovascular morbidity and mortality has not been determined.

**Clinical Pharmacology/Clinical Studies**  
**Hypertriglyceridemia (Fredrickson Type IV)**

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ON ORIGINAL

The response to atorvastatin in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below. For the atorvastatin-treated patients, median (min, max) baseline TG level was 565

Combined patients with isolated elevated TG: Median (min, max) percent changes from baseline

	Placebo (N=12)	Atorva 10 mg (N=37)	Atorva 20 mg (N=13)	Atorva 80 mg (N=14)
Triglycerides	-12.4	-41.0	-38.7	-51.8
Total-C	-2.3	-28.2	-34.9	-44.4
LDL-C	3.6	-26.5	-30.4	-40.5
HDL-C	3.8	13.8	11.0	7.5
VLDL-C	-1.0	-48.8	-44.6	-62.0
non-HDL-C	-2.8	-33.0	-42.7	-51.5

APPEARS THIS WAY  
ON ORIGINAL

**Indications and Usage**

Lipitor is indicated as an adjunct to diet to reduce elevated total-C, LDL-C apo B, and TG levels in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb).

APPEARS THIS WAY  
ON ORIGINAL

Lipitor is indicated as adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson Type IV).

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ON ORIGINAL

Lipitor is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable.

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ON ORIGINAL

Lipitor has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson Types I and V).

APPEARS THIS WAY  
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Proposed labeling for combined S-003/005 is attached and has been conveyed to the sponsor (7-7-98).

**Recommendation**

Pending agreement on labeling, this supplement may be approved.

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

/S/

7-8-98

Recommendation code: AP

cc:

NDA 20-702 Arch

HFD-510

HFD-510: Shen/Simoneau/Parks

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NDA 20-702/S-003 and S-005  
LIPITOR (atorvastatin calcium) tablets  
Parke-Davis

FDA proposed labeling: July 7, 1998

**Clinical Pharmacology**

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**Mechanism of Action**

(the following replaces the last paragraph)

Lipitor reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Lipitor also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Lipitor reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Lipitor reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

APPEARS THIS WAY  
ON ORIGINAL

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma triglycerides (TG) are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, in multivariate analyses, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. The effect of Lipitor on cardiovascular morbidity and mortality has not been determined.

APPEARS THIS WAY  
ON ORIGINAL

**Clinical Studies**

**Hypertriglyceridemia (Fredrickson Type IV)**

The response to atorvastatin in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below. For the atorvastatin-treated patients, median (min, max) baseline TG level was 565

Combined patients with isolated elevated TG: Median (min, max) percent changes from baseline

	Placebo (N=12)	Atorva 10 mg (N=37)	Atorva 20 mg (N=13)	Atorva 80 mg (N=14)
Triglycerides	-12.4	-41.0	-38.7	-51.8
Total-C	-2.3	-28.2	-34.9	-44.4
LDL-C	3.6	-26.5	-30.4	-40.5
HDL-C	3.8	13.8	11.0	7.5
VLDL-C	-1.0	-48.8	-44.6	-62.0
non-HDL-C	-2.8	-33.0	-42.7	-51.5

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**Dysbetalipoproteinemia (Fredrickson Type III)**

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia (Fredrickson Type III) are shown in the table below.

	Median (min, max) at baseline (mg/dL)	median % change (min, max)	
		Atorva 10 mg	Atorva 80 mg
<b>Total-C</b>	442	-37 (-85, 17)	-58 (-90, -31)
<b>Triglycerides</b>	678	-39 (-92, -8)	-53 (-95, -30)
<b>IDL-C + VLDL-C</b>	215	-32 (-76, 9)	-63 (-90, -8)
<b>non-HDL-C</b>	411	-43 (-87, -19)	-64 (-92, -36)

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ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

**Indications and Usage**

Lipitor is indicated as an adjunct to diet to reduce elevated total-C, LDL-C apo B, and TG levels in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb).

APPEARS THIS WAY  
ON ORIGINAL

Lipitor is indicated as adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson Type IV).

APPEARS THIS WAY  
ON ORIGINAL

Lipitor is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.

APPEARS THIS WAY  
ON ORIGINAL

Lipitor is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable.

APPEARS THIS WAY  
ON ORIGINAL

Lipitor has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson Types I and V).

APPEARS THIS WAY  
ON ORIGINAL

Please also remove the follow section from the label: PRECAUTIONS/Drug Interactions/Other Concomitant Therapy.

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ON ORIGINAL

Also, under Adverse Reactions, add the following:

Adverse events associated with Lipitor therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: angioneurotic edema, rhabdomyolysis.

cleared for faxing by .....

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ON ORIGINAL

NDA# 20-702/S-005

LIPITOR (atorvastatin calcium)

Parke-Davis, Ann Arbor, MI

Category: Lipid altering

Proposed new indication: treatment of Type III hyperlipoproteinemia

Date of submission: July 22, 1997 (information amendment date April 27, 1998)

#### Background

Type III hyperlipoproteinemia (familial dysbetalipoproteinemia) occurs at a rate of approximately 1 in 10,000 people and is diagnosed on the basis of elevated total cholesterol and triglycerides in the setting of an abnormal apolipoprotein E phenotype by isoelectric focusing. Specifically, affected individuals carry abnormal allele(s) for apo E and are either homozygous (90%) or heterozygous for apo E2, which, because of its reduced affinity for the LDL receptor, results in impaired clearance of chylomicron and VLDL remnants. In the context of associated metabolic abnormalities, as obesity, Type 2 DM, hypothyroidism, or other monogenic or polygenic dyslipidemias, all sharing the common characteristic of increasing hepatic VLDL production, individuals with these apo E variants develop increased plasma levels of remnant lipoproteins, evident as increased cholesterol, TG, VLDL, IDL, and chylomicrons and by a "broad-beta" pattern on lipoprotein electrophoresis.

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ON ORIGINAL

Remnant hyperlipoproteinemia is associated with accelerated atherosclerosis involving the coronary and peripheral arteries, often more prominent in the latter, and is thus an indication for diet modification with or without lipid altering drug therapy. Current treatment in addition to diet includes fibrates, nicotinic acid, fish oil, and HMGRIs.

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The currently accepted primary therapies for Type III hyperlipoproteinemia, the fibric acid derivatives, acting through PPAR $\alpha$ , increase the expression of lipoprotein lipase (LPL), decrease transcription of the apoC-III gene, and induce transcription of apoA-I and A-II genes. The results of these molecular effects are principally to induce lipolysis of TG on TG-rich lipoprotein remnants (the consequence of increased LPL as well as better accessibility of TG-rich, apoC-III depleted lipoproteins to lipolysis), and to reduce hepatic TG synthesis and thus VLDL production. In the context of adequate synthesis of apoA-I and A-II, lower levels of TG-rich remnants also result in increases in HDL-C. Newer fibrates have an additional effect to lower LDL-C by increased clearance via the LDL receptor. This is felt due to fibrate associated changes in LDL composition and structure that enhance the affinity of LDL for its receptor. Finally, the literature supports changes in the LDL particle phenotype with fibrate therapy from atherogenic, small-dense to less atherogenic, large-buoyant, because lipolysis of VLDL-TG is restored toward normal with these agents.

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In a study of 19 patients with homozygosity for apo E2, simvastatin 20 mg daily for 8 weeks effected changes in total-C, VLCL-C, LDL-C, HDL-C and TG of -41%, -48%, -43%, +26%, and -39%, respectively. Simvastatin 40 mg resulted in additional favorable changes in all lipid parameters. Addition of gemfibrozil 450 mg daily to simvastatin 40 mg daily resulted in modest further reductions in TC, VLDL, and TG, but also reduction HDL-C and increased LDL-C in some patients.

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The current study was designed to assess the effects of two doses of atorvastatin compared to gemfibrozil and simvastatin in a cohort of patients with Type III HLP. The results are submitted in support of changes in labeling in Clinical Pharmacology/Clinical Studies and in Indications and Usage.

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#### Study Design

This was a 32-week, open-label, four-way crossover study of 16 patients. After a 4-8 week dietary lead in, patients were randomized to one of 4 treatment sequences, and received each medication (atorvastatin 10, atorvastatin 80, simvastatin 40, gemfibrozil 1200) for eight weeks. Lipid were measured at baseline and at the end of each treatment period. There were no washout periods in which patients were off all treatments.

Patients had to be \_\_\_\_\_ years old with a TC >250 mg/dL and fasting TG >315 mg/dL on diet. Patients could be either homozygous for apo E2 (E2/E2) or E2/E3 with a ratio of VLDL-C/TG >0.3 at screening.

Patients were excluded with active hepatic disease, secondary causes of HLP, including DM or hypothyroidism, or uncontrolled hypertension.

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The primary efficacy parameters for this investigation were the percent change from baseline in LDL-C and IDL-C + VLDL-C.

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#### Statistical methods

Baseline values were the means of measurements at weeks -2 and 0. For apo CIII and apo E, post-treatment values were the measurements at the ends of the 8-week treatment periods. For the other efficacy parameters, measurements were the average of the values at weeks 6 and 8 of each treatment period, or the average of the last two measurements during a given treatment period.

Comparison across treatments was based on an ANOVA model including the effects of sequence, patient within sequence, treatment, and period.

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#### Patients characteristics

Sixteen patients were randomized and treated. There were 10 men and 6 women. The mean age was 49 years, and 15/16 were white. There were 14 patients with the E2/E2 genotype and 2 patients with E2/E3 genotype.

The table below summarizes the baseline lipid data for the 16 patients.

Table 1. Baseline lipids. N=16

Lipid parameter	mean (SE), mg/dL	median (min, max), mg/dL
total cholesterol	539 (81)	442
triglycerides	1403 (466)	678
HDL-C	35 (2.7)	33
LDL-C	56 (8)	49
IDL-C + VLDL-C	251 (34)	215
non-HDL-C	507 (80)	411

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For a condition with such variable lipid manifestations and in such a small cohort, the median values and minimum and maximum values give a better picture of the patient population. There were two patients with marked elevations of cholesterol and TG at baseline. Their cholesterol levels were 1255 and 1320 and TG levels were 5970 and 5990.

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Four other patients had TG levels ranging from approximately

and cholesterol levels

The remaining ten patients had cholesterol levels above 460 mg/dL. Their TG levels mg/dL.

though with only one patient, with only 3 patients with levels above 470

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#### Disposition

No patients withdrew from the study. The data for patient #4 from the 3<sup>rd</sup> and 4<sup>th</sup> periods of treatment were not included in the efficacy analysis because the order of treatment was inadvertently reversed. These were the gemfibrozil and atorvastatin 10 mg periods, respectively.

## Results

### Efficacy

The goal of treatment in Type III HLP is to lower the burden of apo B-100-containing lipoproteins. This will be reflected in a lowering of the sum of VLDL-C and IDL-C, as these fractions will include the majority of the remnant lipoproteins that contain apo B-100. Perhaps an even better measure of benefit related to reducing the burden of atherogenic lipoproteins, however, is the level of non-HDL-C, simply derived by subtracting the HDL-C level from that of total cholesterol. This is important since an expected benefit derives from lowering LDL-C in addition to levels of remnant lipoproteins.

The tables below summarize the change in key lipid parameters by treatment group. Note that the N for atorvastatin 10 mg and gemfibrozil is 15 and not 16.

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Table 2. Percent change from baseline lipids: median (min, max)

Lipid parameter	Atorva 10 mg n=15	Atorva 80 mg n=16	Gemfibrozil n=15	Simva 40 mg n=16
IDL-C + VLDL-C	-32	-63	-37	-31
non-HDL-C	-43	-64	-31	-45
LDL-C	-8.1	-34	57	-23

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Table 3. Percent change from baseline lipids: mean (SE)

Lipid parameter	Atorva 10 mg	Atorva 80 mg	Gemfibrozil	Simva 40 mg
IDL-C + VLDL-C	-32 (6)	-58 (5)	-31 (10)	-28 (7)*
non-HDL-C	-44 (4)	-64 (3)	-38 (7)	-46 (4)
LDL-C	22 (23)	-7 (18)	89 (36)	10 (18)

As is clear from Table 2, responses were highly variable with all the treatments. For IDL-C + VLDL-C and non-HDL-C, atorvastatin 80 mg showed the greatest mean and median reductions, and was the only treatment with which all patients showed a reduction from baseline. For non-HDL-C, all 16 patients had at least a 36% reduction from baseline. The responses to atorvastatin 10 mg, gemfibrozil, and simvastatin 40 mg were similar for these parameters. Because LDL-C levels tend to rise with gemfibrozil, the response with respect to non-HDL-C is not as marked during that treatment period.

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The following table summarizes the changes from baseline in apolipoproteins B, E, and C-III. ApoC-III is a marker for poorly lipolyzed TG-rich remnant particles (see above).

Table 4. Percent change from baseline for apoB, apoE, and apoC-III: mean (SE)

Apolipoprotein	Atorva 10	Atorva 80	gemfibrozil	Simva 40
total apo B	-46 (5)	-66 (4)	-51 (9)	-52 (5)
total apoE	-26 (6)	-41 (5)	-23 (7)	-20 (6)
apoC-III	-14 (7)	-31 (6)	-11 (12)	-8 (12)

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Again, for each apolipoprotein, atorvastatin 80 mg effected the greatest mean reduction from baseline.

The following table summarizes the on-treatment values for IDL-C + VLDL-C and for non-HDL-C by patient. On-treatment values are directly related to percent lowering from baseline, as there were no washout periods and interim baselines determined in this study. The only baseline value is that from the pre-treatment diet lead-in phase of the trial.

Table 5. Individual-patient on-treatment values for IDL-C + VLDL-C and non-HDL-C by treatment

Patient number (apo E phenotype)	Lipid parameter	Atorva 10 mg	Atorva 80 mg	Gemfibrozil	Simva 40 mg
1	IDL-C + VLDL-C				
	non-HDL-C				
2	IDL-C + VLDL-C				
	non-HDL-C				
3	IDL-C + VLDL-C				
	non-HDL-C				
4	IDL-C + VLDL-C				
	non-HDL-C				
5	IDL-C + VLDL-C				
	non-HDL-C				
6	IDL-C + VLDL-C				
	non-HDL-C				
7	IDL-C + VLDL-C				
	non-HDL-C				
8	IDL-C + VLDL-C				
	non-HDL-C				
9	IDL-C + VLDL-C				
	non-HDL-C				
10	IDL-C + VLDL-C				
	non-HDL-C				
11	IDL-C + VLDL-C				
	non-HDL-C				
12	IDL-C + VLDL-C				
	non-HDL-C				
13	IDL-C + VLDL-C				
	non-HDL-C				
14	IDL-C + VLDL-C				
	non-HDL-C				
15	IDL-C + VLDL-C				
	non-HDL-C				
16	IDL-C + VLDL-C				
	non-HDL-C				

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	non-HDL-C	
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From the above, atorvastatin 80 mg generally had the greatest effect to lower levels of IDL-C + VLDL-C and of non-HDL-C.

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In one case (patient #5), gemfibrozil lowered IDL-C + VLDL-C somewhat more than did atorvastatin 80 mg, but the non-HDL-C level on atorvastatin 80 mg was reduced an additional 22% from baseline compared to the level on gemfibrozil.

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Similarly, in patients #6 and #11, the lowering of IDL-C + VLDL-C was somewhat greater on gemfibrozil than on atorvastatin 80 mg, but the non-HDL-C levels were identical on the two drugs, this because of the LDL-raising effect seen with gemfibrozil.

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Finally, in patients 12 and 16, the responses to atorvastatin 10 mg were, paradoxically, slightly greater than those to atorvastatin 80 mg.

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In conclusion, with regard to lowering of IDL-C + VLDL-C and non-HDL-C, two closely correlated measures of atherogenic particle burden in these patients, atorvastatin 80 mg was generally most effective. In a few cases, gemfibrozil 1200 mg daily achieved the same or greater lowering of IDL-C + VLDL-C, but because of the fibrate-associated increase in LDL-C, had no greater effect on non-HDL-C.

#### Safety

No novel safety issues arose in this study.

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#### Discussion and Conclusions

This study confirms the results seen with simvastatin as published and establishes high-dose atorvastatin as a highly effective lipid-altering treatment in patients with Type III HLP. As stated above, HMGRIs are felt to act primarily by increasing expression of the LDL receptor and thus augmenting their clearance. This action unburdens the lipolytic system and enhances the overall clearance of apoB/E-containing lipoproteins.

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As seen in this trial, gemfibrozil, by contrast to the statins and newer fibrates, while lowering levels of TG-rich remnant lipoproteins by the mechanism described earlier, induces increases in LDL-C. For reasons that are not clear, the LDL particles in gemfibrozil-treated patients are not readily cleared by the LDL receptor. Furthermore, it should be remembered that fibrates, unlike HMGRIs, do not induce increased expression of LDL receptors. Thus, with gemfibrozil, at least, LDL-C levels tend to increase somewhat even as remnant levels are falling. The LDL-C levels are generally not markedly elevated, however. Indeed, in this study, the highest on-treatment LDL-C level was 153 mg/dL, on gemfibrozil.

Statin therapy, on the other hand, enhances clearance of LDL through the LDL receptor. As stated above, an apparent secondary effect of this is to increase lipolysis of TG-rich particles. In this study, 5 patients underwent evaluation of triglyceride lipolysis as measured by AUC for TG and retinol palmitate at the end of each treatment period. The changes in AUC for retinol palmitate were similar for atorvastatin 80 mg and gemfibrozil and both were greater than those on atorvastatin 10 mg and simvastatin 40 mg. The changes in AUC for TG were highly variable, though the mean changes were greatest on atorvastatin 80 mg and gemfibrozil. These measures are thought to reflect capacity for post-prandial clearance of TG-rich lipoproteins. It is their prolonged residence in the plasma that established the Type III phenotype.

LDL particle distribution analyses were not performed as part of this study. Based on lipid and lipoprotein levels alone, high-dose atorvastatin was most effective in this small cohort of patients with Type III HLP. Clearly, this study provides more support for adding statins to the choices for therapy in these patients. It is important to note that no data from this study or elsewhere are available on the

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relative merits of the two approaches (fibrates versus statins) with regard to clinical outcomes reflective of an impact on the course of atherosclerosis.

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**Recommendations**

With respect to labeling, because of the great variability in response to treatment, median percent and ranges of percent changes should be cited instead of mean percent changes from baseline. In addition, a similar enumeration of the effects on non-HDL-C should also be included. The breakdown of the study population by apoE phenotype should be stated. Finally, the disclaimer in approved labeling regarding the absence of data on the cardiovascular morbidity and mortality benefits of LIPITOR treatment should follow the statement of the effect of LIPITOR to lower IDL-C in patients with dysbetalipoproteinemia.

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Suggested language for Clinical Pharmacology/Clinical Studies follows:

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia (Fredrickson Type III) are shown in the table.

	Median (min, max) at baseline (mg/dL)	median % change (min, max)	
		Atorva 10 mg	Atorva 80 mg
Total-C	442	-37	-58
TG	678	-39	-53
IDL-C + VLDL-C	215	-32	-63
non-HDL-C	411	-43	-64

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Proposed labeling for this and for S-003 is attached and has been conveyed to the sponsor (7-7-98).

Pending agreement on labeling, this supplement may be approved.

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

/S/  
7-8-98

Recommendation code: AP  
cc:  
NDA Arch 20-702  
HFD-510  
HFD-510: Herman/Simoneau

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