NDA 20702

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-702

DEC 17 1996

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Byron Scott, R.Ph.
Director, Worldwide Regulatory Affairs
P.O. Box 1047
Ann Arbor, Michigan 48106-1047

Dear Mr. Scott:

Please refer to your June 17, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lipitor™ (atorvastatin calcium) Tablets, 10, 20, and 40 mg.

We acknowledge receipt of your amendments dated July 16 and 30, August 5, 21, and 27, September 3, 11, and 17 (2), October 8 (2), 9, 16, 23 (2), 25 (3), 29, and 31, November 5, 6, 8, 15, 22, 26 (2), and 27 (2), and December 2, 9, 13, and 17 (3), 1996.

This new drug application provides for the use of Lipitor 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). 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 (e.g., LDL apheresis) or if such treatments are unavailable.

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

The final printed labeling (FPL) must be identical to the draft physician labeling (Revision 9) submitted on December 17, 1996, and the draft carton and container labels submitted on October 31 and November 8, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

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

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

We remind you of your Phase 4 commitments specified in your submissions dated November 8, 15, and 27, 1996. These commitments, along with the completion dates agreed upon, are listed below. Protocols, data, and final reports should be submitted to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

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

If you have any questions, please contact:

Julie Rhee
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

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

ITEM 13.1.
Atorvastatin 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)

US Patent Number:	4,681,893
Expiration Date:	May 30, 2006
Patent Type:	Product (generic)
Assignee:	Warner-Lambert Company

US Patent Number:	5,273,995
Expiration Date:	December 28, 2010
Patent Type:	Product (pure isomer)
Assignee:	Warner-Lambert Company

US Patent Number:	5,385,929
Expiration Date:	May 4, 2014
Patent Type:	Product (active metabolite)
Assignee:	Warner-Lambert Company

EXCLUSIVITY SUMMARY for NDA # 20-702 SUPPL # _____

Trade Name Lipitor Generic Name atorvastatin calcium

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 /_X__/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X__/

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

   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 /_X__/ 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 /_X_/

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

_____.

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 /_X__/

If yes, NDA # _____ Drug Name _____

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

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

YES /___/ NO /_X__/

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).

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•/_X__/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

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 /___/

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 /___/

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 # _____

Investigation #2, Study # _____

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 #__, Study # _____

Investigation #__, Study # _____

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 _____

_____ | _____

_____ | _____

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: _____

_____

_____

_____

Julia Rhee
Signature
Title: Consumer Safety Officer

Nov. 18, 1996
Date

Signature of Division Director

11-24-96
Date

cc: Original NDA Division File HFD-~~85~~ 93 Mary Ann Holovac

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-702 Trade (generic) names Lipitor (atorvastatin) Tablets

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. 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 do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

#4. The only use in children will be as adjunctive therapy in homozygous FH, an extremely rare condition. It is not feasible to conduct safety studies in this small group of patients.

_____ 11-15-96
Signature of Preparer Date

cc: Orig NDA
HFD-[illegible] /Div File
NDA Action Package

ITEM 13.3.

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.

Medical Officer's review of NDA
NDA # 20-702
NDA submission date: 6-17-96 (4-month safety update submitted 10-17-96)
review completed: 10-28-96

Drug name: Atorvastatin calcium
Proposed trade name: Lipitor
Chemical name: [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methlyethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

Sponsor: Parke-Davis , Ann Arbor, MI

Pharmacologic category: HMG-CoA reductase inhibitor
Proposed indication: treatment of hypercholesterolemia

Dosage forms: 10, 20, 40 mg, oral

Related drugs: lovastatin, simvastatin, pravastatin, fluvastatin

Medical Reviewer: David G. Orloff, M.D.
Statistical input: Joy Mele, M.S.

This review consists of 139 pages and 1 attachment
Attachment: Atorvastatin proposed label with recommended revisions

Table of Contents

Section 1 Materials reviewed:
Volumes 1.1, 1.2, 1.29-1.31, 1.124-1.165, 4-month safety update

NDA 20-702 was submitted as a CANDA. The medical review was virtually completely restricted to the CANDA materials. Fewer than 10 volumes were also reviewed in paper format. The focus of this review was on Section 8 (Clinical data). Cursory review of specific portions of the chemistry, pharmacology, and pharmacokinetics sections was also undertaken. Narratives for deaths, discontinuations due to adverse events, and clinically important ALT/AST and CPK abnormalities were also reviewed.

Section 2:

2.1 Background

Cholesterol balance and synthesis inhibitors

Cholesterol is an integral component of all membranes, a precursor in the synthesis of steroid hormones, and likely rate limiting in the synthesis and assembly of VLDL particles that, in native and modified forms, transport cholesterol and TG from the liver, the principal site of cholesterol biosynthesis, to peripheral tissues.

Cholesterol enters the body from two sources. One third is from dietary consumption, and two thirds are endogenously synthesized, for the most part in the liver. As such, cholesterol lowering therapies have largely been directed at reducing endogenous synthesis. Liver selective agents are potentially the most useful and least toxic to non-lipoprotein synthesizing tissues.

Early attempts at inhibiting hepatic cholesterol synthesis were unsuccessful because of adverse effects of the drugs employed. Triparanol (MER-29), a compound that inhibits cholesterol synthesis distally in the biosynthetic pathway, had serious toxicity including cataracts, ichthyosis, and alopecia, which were attributed to the accumulation of desmosterol. Other late-stage inhibitors also led to accumulation of non-metabolizable steroid intermediates in peripheral tissues and caused cataracts in animals.

HMG-CoA reductase inhibitors

Agents targeted more proximally in the pathway were ultimately successful in therapeutic intervention. The most effective cholesterol lowering agents currently available belong to the class of HMG-CoA reductase inhibitors (HMGRIs). HMG-CoA reductase is the rate-limiting enzyme in cholesterol biosynthesis. By inhibiting hepatic cholesterol synthesis at this enzymatic step and thereby diminishing intracellular pools, the expression of cell-surface LDL receptors is up-regulated and clearance of LDL-C, the major lipoprotein of human plasma, is augmented. For many patients with primary hypercholesterolemia (Fredrickson Type II a) and mixed dyslipidemia (Type II b), HMGRI therapy thus effects a steady state reduction in plasma total and LDL-C.

The first HMGRI studied, mevastatin, caused neoplastic changes in intestinal lymph tissue of dogs. Lovastatin, which followed, had no such toxicities. Both lovastatin and fluvastatin, however, did cause cataracts in dogs, though at high doses. The incidence was correlated with plasma levels of drug but not with duration of treatment or degree of lipid lowering. Plasma levels of the magnitude seen in dogs developing cataracts are never observed in humans receiving maximum doses of either drug. Indeed, few if any cases of cataracts have been attributed to HMGRIs to date, though vigilance continues to be paid to the issue in clinical testing of new agents in the class.

HMG-CoA reductase catalyzes the synthesis of mevalonate from two molecules of HMG-CoA, which is then further metabolized in a series of enzymatic steps to cholesterol. Mevalonate is an intermediate not only in the pathway to cholesterol, but also in the synthesis of the prenyl,

geranyl, and farnesyl pyrophosphate (used in post-translational modification of proteins), ubiquinones (components of the electron transport chain and critical in energy metabolism), dolichols (used in the maturation of glycoproteins), and isopentenyl adenine (a component of tRNA). Cellular depletion of any or all of these metabolic products could theoretically be deleterious.

The safety and efficacy of the class (including 4 members marketed in the US) has been established over nearly a decade of market use as well as in a number of large-scale, long-term, controlled clinical trials. Notably, cholesterol lowering by individual members of this class has been shown to reduce the risk of new onset CHD, of recurrent CHD events (both fatal and non-fatal) in patients with both elevated and average cholesterol levels at baseline. Most importantly, in these same clinical trials, no excess non-cardiovascular mortality has been attributed to these agents.

Toxicity of HMGRIs

The spectrum of adverse events attributed to the drugs include effects on liver and muscle with attendant elevation in tissue enzymes, and sleep disturbances. Hepatic effects, manifest as transient, intermittent, mild elevations in transaminases, most frequently without cholestasis, are common in patients taking HMGRIs chronically, and appear to be dose-related. Marked elevations in transaminases, far less common (<1%) and usually asymptomatic, also perhaps dose-related, are felt to be potentially serious. Withdrawal of drug or reduction in dose results in resolution of the abnormalities.

The most serious adverse effects of the HMGRIs are manifest in muscle and cover a spectrum from mild asymptomatic elevations in CPK to marked elevations with muscle pain and tenderness to frank rhabdomyolysis. Serious muscle toxicity, usually idiosyncratic in nature, occurs extremely rarely (<<1%) in patients taking HMGRIs alone. The risk is felt to be significantly increased by concomitant use of drugs that inhibit the metabolism of the HMGRIs. Drugs as the fibrates, erythromycin, cyclosporine, and itraconazole all inhibit cytochrome P-450 isoenzyme CYP3A4. As a result, systemic levels of HMGRIs are increased, resulting in greater toxicity.

Both hepatic and muscle effects of the HMGRIs are felt to be related to the mechanism of action of the drug. One hypothesis for the myopathic effects is depletion of mitochondrial ubiquinone (coenzyme Q) with resultant disruption of cellular energy metabolism. This has not been conclusively proven.

Another potential adverse effect of inhibition of cholesterol biosynthesis is impairment of function of steroidogenic tissues, adrenal, testis, and ovary. The first has been most extensively studied. Adrenal steroidogenesis is proposed by most to utilize two sources of cholesterol. The first, and that required for acute increases in adrenal steroid production, for example under stress or in the setting of an ACTH stimulation test, is the intracellular pool of cholesterol ester. The second source, required for maintenance of steroid synthesis, is cholesterol as part of LDL taken up by the adrenal cell via LDL receptors. Patients with hypo- and abetalipoproteinemia and with

homozygous FH and absent LDL receptor function have reduced cortisol responses ACTH, supporting a role for uptake of LDL-C in the maintenance of intracellular pools.

The effect of HMGRIs on adrenal and gonadal steroidogenesis has been studied in the past, with an initial report suggesting an effect of simvastatin to decrease the peak cortisol response to ACTH. Other studies have failed to replicate this finding or to document impaired gonadal steroidogenesis in patients treated with simvastatin or pravastatin for up to 36 months.

Recently, a third possible source of cholesterol for adrenal tissue has been described. This is a "docking" receptor for HDL, heretofore unknown, that allows HDL to deliver some of its cholesterol esters to cells without being internalized and catabolized. Indeed, this novel receptor is expressed (perhaps exclusively) in steroidogenic tissues. It is conceivable that this mechanism accounts for the lack of effect of the HMGRIs on adrenal reserve.

Finally, as before mentioned, initial concern over the role of these agents in cataract formation have not been borne out.

Atorvastatin

The HMGRI which is the subject of this NDA, atorvastatin, is a tissue selective, hydrophilic compound with a relatively high specificity for liver. It possesses a unique chemical structure unrelated to the existing HMGRIs and it administered as the hydroxyacid, or active, form. It effectively lowers LDL-C and TG in plasma by inhibiting HMG-CoA reductase in the liver and reducing hepatic VLDL synthesis as well as by increasing clearance of LDL-C via the LDL receptor. With the exception of HDL-C, it reduces cholesterol and TG in all lipoprotein fractions. It has a long duration of action in the liver, which is thought to further contribute to its unique lipid lowering effects.

NDA 20-702 includes data from preclinical studies that have addressed adequately the toxicological issues relevant to the class. In addition, the results of clinical pharmacology studies involving 590 atorvastatin-treated healthy volunteers and 21 completed clinical studies involving 2502 patients treated with atorvastatin are presented. The efficacy of the drug has been demonstrated in patients with Types II a, II b, and IV hyperlipoproteinemia and has been shown to lower LDL-C in a dose-related manner and TG in a consistent, non-dose-related fashion. Furthermore, atorvastatin has been shown to have efficacy in a high percentage of patients studied with homozygous familial hypercholesterolemia, including some with absent LDL receptor function. The efficacy of the drug exceeds that of marketed HMGRIs, based both on head-to-head comparison and on historical information. The safety of the drug has been probed with adverse event monitoring, laboratory testing including tests of adrenal reserve, and in ophthalmologic follow up. The toxicities of the drug are consistent with other members of the class. Specifically, liver and muscle effects were observed, the former dose-related in incidence. No impairment of adrenal function was observed and there were no effects on the eye.

2.2 NDA 20-702: Administrative history

An IND for atorvastatin for the treatment of patients with dyslipidemia was submitted to FDA September 28, 1990 (IND). A treatment IND to allow treatment of patients with homozygous familial hypercholesterolemia with atorvastatin was granted February 9, 1995.

Eight meetings between FDA and Parke-Davis occurred during the development of atorvastatin and are briefly outlined below:

June 24, 1993. Representatives of Parke-Davis met with FDA (Division of Metabolism and Endocrine Drug Products) to discuss the atorvastatin clinical development program.

December 16, 1993. An End-of-Phase 2 Meeting for atorvastatin was held between FDA and Parke-Davis representatives.

October 19, 1994. Representatives of Parke-Davis met with FDA to discuss the feasibility and mechanics of submitting an electronic version of the NDA (e.g., CANDA).

November 30, 1994. Parke-Davis representatives met with FDA to discuss outcome studies and proposed outcome statements suggested for use in promotion.

April 4, 1995. A pre-NDA meeting to discuss atorvastatin Chemistry, Manufacturing, and Controls was held between FDA and Parke-Davis April 4, 1995.

June 20, 1995. Representatives of Parke-Davis met with FDA to discuss the change in the physical state for atorvastatin drug substance from amorphous to crystalline.

September 7, 1995. A Pre-NDA meeting for atorvastatin was held between FDA and Parke-Davis representatives.

November 13, 1995 Representatives of Parke-Davis met with FDA to provide a demonstration of the CANDA.

2.3 Atorvastatin: Proposed indications, dosage, timing

The recommended dose of atorvastatin is 10 to 80 mg once daily, any time of day, with or without food. The drug is recommended for use in patients with heterozygous familial and nonfamilial hypercholesterolemia and mixed dyslipidemia as well as in patients with homozygous familial hypercholesterolemia. The label recommends dosage adjustment based on lipid levels every 2 to 4 weeks.

No dosage adjustments are recommended for patients with renal insufficiency.

With regard to hepatotoxicity and underlying hepatic dysfunction, the label recommends the

following:

Liver function tests should be performed before the initiation of treatment, at 8 to 12 weeks, and periodically (e.g., every 6 months) thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 × ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin

With regard to muscle toxicity, the label recommends the following:
The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

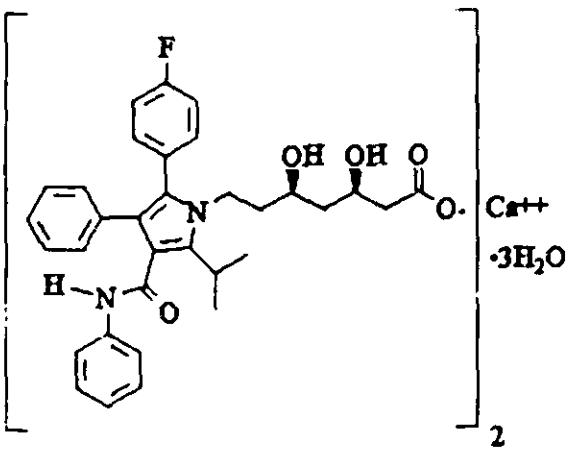
ATORVASTATIN THERAPY SHOULD BE TEMPORARILY WITHHELD OR DISCONTINUED IN ANY PATIENT WITH AN ACUTE, SERIOUS CONDITION SUGGESTIVE OF A MYOPATHY OR HAVING A RISK FACTOR PREDISPOSING TO THE DEVELOPMENT OF RENAL FAILURE SECONDARY TO RHABDOMYOLYSIS, (E.G., SEVERE ACUTE INFECTION, HYPOTENSION, MAJOR SURGERY, TRAUMA, SEVERE METABOLIC, ENDOCRINE AND ELECTROLYTE DISORDERS, AND UNCONTROLLED SEIZURES).

Foreign marketing
As of the filing of the NDA, atorvastatin was not marketed anywhere in the world.

APPEARS THIS WAY
ON ORIGINAL

Section 3

Chemistry:



The chemical structure and molecular weight of atorvastatin calcium are shown below.

Molecular Formulae and Weights

Anhydrous calcium salt	$(C_{33}H_{34}FN_2O_5)_2Ca$	1155.38
Calcium salt trihydrate	$(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$	1209.42
Free acid	$C_{33}H_{35}FN_2O_5$	558.66

Generic Name

Atorvastatin calcium (USAN)

Chemical Name

[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

Amorphous and crystalline forms of atorvastatin:

The drug substance has been isolated in amorphous and crystalline forms. Development activities were conducted using the amorphous and the thermodynamically most stable crystalline form. The form of the drug substance intended for commercial use is the most stable crystalline form

which exi[illegible] stalline trihydrate (see above).

The aque[illegible] lity profiles of the two physical forms are identical, as shown below.

TABLE 3.1. Atorvastatin Calcium Solubility in Aqueous Solutions, 37°C

Solvent	Equilibrium solubility (mg/mL)	
	Amorphous	Crystalline
Water	0.12	0.11
0.1N HCl	0.01	0.01
0.05 M Sodium Phosphate, pH 7.4	0.72	0.70

There are no obvious aspects of the chemical characteristics of crystalline versus amorphous atorvastatin that predict any clinical implications.

Section 4
Animal pharmacology of atorvastatin:

The hypolipidemic potential of atorvastatin was evaluated in normocholesterolemic animals, models of diet-induced hypercholesterolemia, and a model of LDL receptor deficiency. Underlying mechanisms responsible for the observed reductions in plasma cholesterol such as the effect of atorvastatin on the regulation of lipoprotein production, secretion and clearance, sterol synthesis as assessed in vivo and in vitro, and potency of HMG-CoA reductase inhibition were evaluated. The hypotriglyceridemic activity of atorvastatin was assessed in LDL receptor-deficient mice, normocholesterolemic rats and guinea pigs, a diet-induced model of hypertriglyceridemia, and hypercholesterolemic rabbits and miniature pigs. Finally, the antiatherosclerotic potential of atorvastatin was determined in models of atherosclerotic lesion progression and regression.

4.1 Cholesterol Lowering Potential in Various Species

Cholesterol Lowering in LDL Receptor-Deficient Mice
Atorvastatin lowers plasma total and LDL-C levels and hepatic VLDL-cholesterol (VLDL-C) secretion, i.e., plasma cholesterol production, in LDL receptor-deficient mice.

Cholesterol Lowering in Rats
Atorvastatin lowers plasma cholesterol in chow-fed rats after 2 weeks of administration irrespective of whether the compound was admixed in the diet or administered by oral gavage.

Cholesterol Lowering in Guinea Pigs
Atorvastatin was evaluated in guinea pigs, a model in which LDL is the major lipoprotein, to determine the compound's effect on plasma total and lipoprotein cholesterol. At 30 mg/kg, the reduction in total cholesterol with atorvastatin and lovastatin was due primarily to a 49% and 27% decrease in LDL-C, respectively, but atorvastatin also significantly reduced VLDL-C by 47%. The reduction in plasma total and lipoprotein cholesterol levels observed in guinea pigs with atorvastatin is associated with an alteration in lipoprotein composition, a reduction in apo B secretion, and an increase in hepatic LDL microsomal binding.

Cholesterol Lowering in Rabbits
The ability of atorvastatin to lower plasma total and lipoprotein cholesterol levels was also evaluated in 2 rabbit models of hypercholesterolemia. The endogenous hypercholesterolemic (EH) rabbit is a dietary model of reduced clearance and over-production of lipoproteins in the absence of dietary cholesterol. Most of the plasma cholesterol, i.e., 79% to 85%, is transported in LDL. The cholesterol-fed rabbit is a model of dietary-induced hypercholesterolemia which is characterized by the accumulation of beta-migrating VLDL. In EH and cholesterol-fed rabbits, the hypolipidemic activity was evaluated by mixing atorvastatin into the EH or cholesterol containing diets or a chow-fat diet after hypercholesterolemia was established.

In EH rabbits, after 6 weeks of treatment with 1 to 10 mg/kg/day, atorvastatin dose-dependently

lowered plasma total cholesterol 38% to 54% while a significant 35% reduction was noted with lovastatin at only 10 mg/kg/day. The efficacy noted at the 3-mg/kg/day dose of atorvastatin was due to a 55% decrease in LDL production and 47% reduction in apo B. Lovastatin had no significant effect on LDL production or apo B levels and there was no change in LDL clearance (fractional catabolic rate) with either compound.

In cholesterol-fed rabbits, atorvastatin prevented a diet-induced hypercholesterolemia primarily through a reduction in VLDL-C. After 8 weeks of treatment, atorvastatin, lovastatin, pravastatin, and simvastatin admixed at 2.5 mg/kg in the cholesterol/fat diet lowered plasma total cholesterol levels 45%, 47%, 33%, and 60%, respectively, due to a 38% to 71% decrease in VLDL-C.

Cholesterol Lowering in Dogs
Atorvastatin dose-dependently lowered plasma total cholesterol 15% to 41% in cholestyramine-primed dogs over the dose range of 0.3 to 10 mg/kg. Cholesterol reductions observed with atorvastatin were comparable to lovastatin.

Cholesterol Lowering in Miniature Pigs
In cholesterol-fed miniature pigs, atorvastatin significantly reduced plasma total and LDL-C and VLDL and LDL apo B levels due primarily to a decrease in VLDL and LDL apo B production rates. The fractional catabolic rate and lipid composition of VLDL and LDL were unchanged by atorvastatin.

4.2 Studies Related to Mechanism of Action

Alterations in Apo B Metabolism
As noted above, atorvastatin significantly lowered plasma total and lipoprotein cholesterol and apo B in several animal models of hypercholesterolemia. These in vivo efficacy studies and lipoprotein kinetic studies suggested that atorvastatin altered the production and secretion of apo B in the liver. A series of in vitro studies were performed in cultured Hep-G2 cells, a human hepatocyte cell line, in order to assess the effect of atorvastatin (sodium) on secretion, degradation, and translocation of apo B.

In Hep-G2 cells, atorvastatin reduced the oleate-stimulated secretion of apo B by 21% and decreased the amount of intracellular apo B remaining within the cells by 25%, suggestive of a stimulation in apo B degradation. Atorvastatin increased the intracellular degradation of apo B in permeabilized Hep-G2 cells. Atorvastatin significantly increased the fraction of apo B degraded. The rate of apo B degradation was also increased by atorvastatin. Lovastatin at the same concentration had no effect on apo B degradation or rate of degradation.
Associated with the observed increase in apo B degradation was a reduction in apo B translocation.

In summary, based on these in vitro studies in Hep-G2 cells, 1 mechanism contributing to the observed in vivo efficacy may be that atorvastatin uniquely reduces the production of apo B by limiting the availability of cholesterol necessary to protect apo B from proteolytic degradation

and thereby limit apo B translocation into the ER. The reduction in apo B secretion may be a result of enhanced degradation and impaired apo B assembly into lipoprotein particles.

4.3 Alterations in Sterol Synthesis

The ability of atorvastatin and metabolites to inhibit sterol synthesis was assessed in rats using several methodologic approaches. Qualitatively all agents were relatively equipotent except for fluvastatin which appeared 10-fold more

Atorvastatin primarily inhibits liver sterol synthesis; however, modest inhibition was observed in such nonhepatic tissues as the spleen and adrenal. At doses of atorvastatin sufficient to inhibit hepatic sterol synthesis by >90%, no change in sterol synthesis was noted in the testis, kidney, muscle, and brain. In contrast, lovastatin at doses with similar hepatic effects inhibited splenic, adrenal, and kidney sterol synthesis by 50% to 70% without significantly affecting the testis, muscle, and brain. Pravastatin at doses inhibiting hepatic sterol synthesis only reduced kidney sterol synthesis by 43%.

Specific Inhibition of Sterol Synthesis In vitro

Specific inhibition of sterol synthesis by atorvastatin or atorvastatin (sodium) was assessed in liver microsomal homogenates, cultured rat hepatocytes, human fibroblasts and 1 mm cubes of rat liver, spleen, and testis. Partitioning of atorvastatin into model membranes was evaluated as a potential mechanism for the observed in vitro potency.

In a partially purified rat liver microsomal homogenate, atorvastatin was 4 times more potent than the racemic form of atorvastatin and there was no statistically significant difference in potency of atorvastatin relative to lovastatin, pravastatin, and fluvastatin.

In cultured rat hepatocytes, the potency of atorvastatin was not markedly different from lovastatin, pravastatin, and fluvastatin. In contrast, in cultured human skin fibroblasts atorvastatin was moderately potent, lovastatin, and fluvastatin were the most potent while pravastatin was the least potent.

The effect of atorvastatin (sodium) on sterol synthesis was also evaluated relative to sodium salt of the parent acid of lovastatin, pravastatin, and fluvastatin in 1 mm cubes of rat liver, spleen, and testis. Atorvastatin (sodium) was equipotent in the liver to lovastatin and approximately 4 times more potent than fluvastatin or pravastatin. In the spleen and testis, atorvastatin (sodium) was approximately 6 to 9 times less potent than lovastatin and 8 to 9 times more potent than pravastatin. Relative to fluvastatin, atorvastatin (sodium) was 10 times more potent in the spleen and 9 times less potent in the testis.

4.5 Specific Inhibition of HMG-CoA Reductase In vitro

Specific inhibition of HMG-CoA reductase by atorvastatin (sodium) was assessed by measuring the incorporation of radiolabeled HMG-CoA into mevalonate.

Atorvastatin was equipotent to lovastatin and simvastatin and 2 to 6 times more potent than

pravastatin and fluvastatin at inhibition of HMG-CoA reductase. The sodium and calcium salts of the parent acid of atorvastatin, the ortho-hydroxy metabolite, and the para-hydroxy metabolite were relatively equipotent when evaluated in the same assay.

4.5 Pharmacological Effects Related to the Treatment of Hypertriglyceridemia
The hypotriglyceridemic effect of atorvastatin was evaluated in LDL receptor-deficient mice and both chow-fed and sucrose-fed rats. Plasma triglyceride levels were also examined in the models of hypercholesterolemia noted earlier.

Atorvastatin reduced plasma triglyceride levels 10% to 39% in male and female LDL receptor-deficient mice, and the changes were unrelated to dose and plasma triglyceride production rates. Atorvastatin lowered plasma triglycerides in chow-fed rats irrespective of whether the compound was admixed in the diet or administered by oral gavage for 2 weeks. Although fluvastatin at comparable doses and plasma drug levels reduced plasma triglyceride levels, mortality was observed.

Atorvastatin reduced both the plasma triglycerides and triglyceride secretion rates in the sucrose-fed rat, a model of hypertriglyceridemia due to enhanced VLDL triglyceride production.

Changes in plasma triglyceride levels were also noted in guinea pigs, rabbits, and miniature swine.

4.6 Pharmacological Effects Related to the Treatment of Atherosclerosis
The antiatherosclerotic potential of atorvastatin was assessed in two rabbit models of atherosclerosis. A common feature of the models is that atherosclerotic lesions were induced by a combination of hypercholesterolemia and chronic endothelial denudation. The models differ in the time of atorvastatin administration and manner in which atorvastatin was administered. In the first model, atorvastatin was administered in a cholesterol-rich diet coincident with induction of atherosclerotic lesions. In the second model, atorvastatin was given in a low cholesterol, low-fat diet to animals with pre-established atherosclerotic lesions whose plasma total cholesterol levels were nearly normalized by diet prior to drug intervention.

Atorvastatin can attenuate the development and cholesteryl ester enrichment of atherosclerotic lesions when administered coincident with lesion induction. Total cholesterol levels in this rabbit model were reduced 53% to 60% due primarily to a reduction in plasma VLDL-C. The lipid content of the iliac-femoral artery was unaffected by atorvastatin; however, atorvastatin significantly reduced the thoracic aortic cholesteryl ester content by 55% and free cholesterol content 45%. Simvastatin had a similar effect while lovastatin and pravastatin had no effect. Atorvastatin significantly decreased the cross-sectional area and monocyte-macrophage content of certain lesions. In the descending thoracic aorta, a site of spontaneous, diet-induced atherosclerotic lesions, atorvastatin significantly reduced the percentage of grossly discernible atherosclerotic lesions.

The ability of atorvastatin to blunt the development of complex atherosclerotic lesions and

promote regression of a lipid-enriched lesion was assessed in an additional rabbit model of atherosclerosis. The second model of atherosclerosis consisted of a lesion induction phase of 15 weeks followed by an 8-week drug intervention phase. In this model, plasma total cholesterol levels were reduced 43% relative to control animals fed the chow/fat diet and the reduction was due to a 47% to 50% decrease in both VLDL-C and LDL-C. Relative to the untreated control, atorvastatin reduced the cholesteryl ester enrichment of the iliac-femoral artery and thoracic aorta by 27% to 41% without changing the gross extent of thoracic aortic lesions and incidence of fibrous plaques. As evidence of early lesion regression, atorvastatin reduced the cholesteryl ester content of the iliac-femoral artery by 37% relative to initiation of drug intervention, i.e., a group of animals necropsied prior to drug treatment. Morphometric analysis of the iliac-femoral artery revealed that atorvastatin reduced the lesion cross-sectional area by 40% and monocyte-macrophage content by 60%. Within the aortic arch, atorvastatin had no effect on lesion cross-sectional area and monocyte-macrophage content and this observation is consistent with results obtained with atorvastatin when the compound was administered coincident with lesion initiation.

4.7 Pharmacological Actions Related to Possible Adverse Effects

Atorvastatin or atorvastatin (sodium) was evaluated in studies designed to relate other pharmacological actions to possible adverse effects. Atorvastatin was used in central nervous system (CNS), cardiovascular/respiratory, antithrombocyte aggregation, gastrointestinal, genitourinary, endocrine safety tests, isolated organ preparations, and in the studies related to measurement of serum enzyme effects.

Central Nervous System (CNS) Safety Tests

The CNS safety assessment of atorvastatin was performed in mice after oral and intraperitoneal administration. Atorvastatin had no significant effect on locomotor activity or coordination when compared to placebo.

Atorvastatin was tested to observe overt CNS signs and general appearance. No significant overt effects were observed in the short term or during the 96 hours after treatment at any of the doses.

In mice, atorvastatin had no effect on pentobarbital induced sleeping time, no anticonvulsant or seizure-precipitating activity as noted by electric shock- or pentylenetetrazol-induced seizure threshold or no antinociceptive or hyperalgesic effect in response to tail pinch or acetic acid stimuli.

Atorvastatin was evaluated in rats to assess the effects on hyperphagia, locomotion and general CNS effects. No change in locomotion was apparent after 9 consecutive doses. No differences in food consumption or body weight gain were observed with atorvastatin or lovastatin. No overt CNS signs were observed.

Atorvastatin relative to lovastatin was evaluated for effects on the sleep-awake cycle of rats. Electroencephalograms (EEG) and electromyograms (EMG) were monitored as a measure of either awake, slow-wave-sleep or rapid-eye-movement sleep. No significant decreases in sleep durations or increases in sleep latencies following acute or chronic dosing of either compound

were observed.

Atorvastatin administered to rats had no effect on body temperature, neocortical and hippocampal EEG activities, grip strength, or coordinative motion.

Cardiovascular/Respiratory Safety Test
Atorvastatin was evaluated for effects on heart rate and blood pressure in normotensive male rats. In conscious normotensive rats dosed orally for 4 consecutive days with atorvastatin in rising doses of 1, 3, 10, and 30 mg/kg, there were no effects on either blood pressure or heart rate at any dose. Oral administration to rats of 10, 30, and 100 mg/kg atorvastatin had no effect on platelet aggregation, prothrombin time, activated partial thromboplastin time, thrombin time, and on osmotic pressures associated with the starting, maximum, and ending points of hemolysis.

Atorvastatin had no significant effect on mean blood pressure, heart rate, left ventricular pressure, cardiac output, and total peripheral resistance in dogs. No overt behavioral changes were noted.

Atorvastatin administered to dogs had no acute effects on blood flow, ECG, norepinephrine-induced hypertension, acetylcholine-induced hypotension, or respiration rate.

In dogs, atorvastatin did not produce any significant changes in pulmonary parameters such as total pulmonary resistance, dynamic compliance, tidal volume, respiratory rate, and minute volume or in mean arterial blood pressure and heart rate up to a cumulative dose of 14.4 mg/kg.

The effect of atorvastatin on platelet aggregability in humans was also assessed in vitro. Atorvastatin had no effect on in vitro aggregation of human platelets at doses up to 1 mM.

In isolated organ bath preparations, atorvastatin at 0.1, 1, and 10 μM had no effect on norepinephrine-induced contraction of rat aorta, electrically-induced contraction of rat diaphragm, basal or isoproterenol-induced contraction of guinea pig atria, and basal or histamine-induced contraction of guinea pig trachea.

Gastrointestinal Safety Test
After single and 7 daily doses of 10, 30, and 100 mg/kg atorvastatin in mice, gastrointestinal motility was unaffected.

Atorvastatin administered to rats for 1 and 7 days at 10, 30, and 100 mg/kg had no effect on the volume and acidity of gastric juice or bile volume.

In isolated organ bath preparations, atorvastatin at 0.1, 1, and 10 μM had no effect on basal and 5-hydroxytryptamine hydrochloride-induced contraction of rat gastric fundus or acetylcholine- and barium-induced contraction of guinea pig ileum.

Genitourinary Safety Test
A single dose of 10, 30, and 100 mg/kg atorvastatin in rats had no effect on urine volume excreted, electrolytes, i.e., Na+, K+ or Cl-, pH, or osmotic pressure in urine of rats. In isolated

organ bath preparations, atorvastatin had no effect on basal, electrical- and norepinephrine-induced contractions of the guinea pig vas deferens. Contraction force and frequency of pregnant and nonpregnant rat uteri were also unaffected by atorvastatin.

Endocrine Safety Test
Following single and 7 daily doses of 10, 30, and 100 mg/kg atorvastatin in rats plasma levels of testosterone and corticosterone were unaffected.

Serum Enzyme Effects
As part of studies designed to determine the effect of atorvastatin on plasma total cholesterol and triglyceride levels, serum enzyme levels were measured. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine phosphokinase (CPK), and lactate dehydrogenase (LDH) were monitored. In rats, plasma AST and ALT levels were elevated approximately 2-fold at the 100-mg/kg dose when atorvastatin was added to the diet but no changes in CPK and LDH were noted. Plasma atorvastatin equivalents were 0.12 and 1.44 µg eq/mL at the 25- and 100-mg/kg dose, respectively. For comparison, lovastatin at doses of 25 and 100 mg/kg had no effect the various plasma enzyme levels; however, plasma lovastatin equivalents were 0.42 to 0.46 µg eq/mL and dose independent. Fluvastatin at 25 mg/kg administered by oral gavage elevated plasma AST and ALT levels; however, mortality was noted at both 25 and 100 mg/kg. Plasma fluvastatin equivalents, were approximately 2 µg eq/mL.

The combination of atorvastatin and gemfibrozil was evaluated in the chow-fed rat.
Rats were fed atorvastatin and gemfibrozil in chow either alone at 25, 100, and 200 mg/kg or in combination at 25 and 100 mg/kg each. Atorvastatin increased plasma AST levels 203% at the 200-mg/kg dose while no significant changes in CPK or ALT were noted. Gemfibrozil alone or in combination with atorvastatin had no effect on plasma enzyme levels.

Summary:

Underlying mechanisms responsible for the observed reductions in plasma cholesterol were evaluated by the sponsor. Some of the findings may explain the increased efficacy of atorvastatin over marketed HMGRIs in lowering LDL-C and triglyceride and the apparently unique activity of atorvastatin in FH homozygotes, including those with LDL receptor activity. Atorvastatin reduced the secretion of apo B from HEP-G2 cells, a human hepatocyte cell line, by increasing the intracellular degradation of apo B and impairing the translocation of apo B into the lumen of the endoplasmic reticulum. Atorvastatin is a potent inhibitor of sterol synthesis in vivo and primarily inhibits liver sterol synthesis; however, modest inhibition was observed in such nonhepatic tissues as the spleen and adrenal.

The comparison of atorvastatin to other HMGRIs was also addressed by the sponsor. Specific inhibition of sterol synthesis by atorvastatin or atorvastatin (sodium) and other agents was assessed in liver microsomal homogenates, cultured rat hepatocytes, human fibroblasts and 1-mm cubes of rat liver, spleen, and testis. In a partially purified rat liver microsomal homogenate,

atorvastatin and atorvastatin (sodium) were comparable in potency to lovastatin, pravastatin, and fluvastatin. In cultured rat hepatocytes, the potency of atorvastatin was not markedly different from lovastatin, pravastatin, and fluvastatin. In contrast, in human skin fibroblast cultures atorvastatin was moderately potent, lovastatin and fluvastatin were the most potent while pravastatin was the least potent. Partitioning of atorvastatin (sodium) into model membranes was assessed and it was determined that atorvastatin rapidly crossed membrane barriers and such transport was minimally affected by membrane cholesterol content.

The antiatherosclerotic potential of atorvastatin was determined in rabbit models of atherosclerotic lesion progression and regression. Atorvastatin can attenuate the development and cholesteryl ester enrichment of atherosclerotic lesions when administered coincident with lesion induction. Atorvastatin can blunt the development of complex atherosclerotic lesions and promote regression of a lipid-enriched lesions.

Atorvastatin or atorvastatin (sodium) was evaluated in studies designed to relate other pharmacological actions to possible adverse effects. Atorvastatin has no substantive effect on the central nervous system, cardiovascular/respiratory system, platelet aggregation, gastrointestinal, genitourinary, or endocrine system.

Finally, in chow-fed rats, plasma AST and ALT levels were elevated approximately 2-fold at 100 mg/kg atorvastatin but no elevations in CPK and LDH were noted.

4.9 Animal toxicology:
See toxicology review for details.

In general, the toxicology of atorvastatin is consistent with that of other members of the drug class. No novel toxic reactions were observed and no novel adverse effects are therefore predicted in clinical use.

A central issue in the toxicology of atorvastatin was the relative toxicity of amorphous and crystalline drug. All initial studies utilized amorphous bulk drug substance. When it was determined crystalline atorvastatin would be the marketed drug form, additional 13-week toxicokinetic studies in mice, rats, and dogs were conducted to compare exposure and toxicity with the 2 forms.

Acute toxicity:
The sponsor concluded the following from the acute oral and intravenous toxicology studies performed using amorphous drug:

The acute toxicity of atorvastatin in rodents is low. Oral median lethal doses (MLD) are greater than 5000 mg/kg.

Liver, intestinal tract, and gallbladder were identified as target organs in dogs given escalating oral doses.

Single IV doses of atorvastatin up to 4 mg/kg are nontoxic to mice, rats, and dogs.

Multidose toxicity:
The results of multidose toxicology studies of varying duration yielded the following conclusions:

Target organs in mice given atorvastatin are adrenal, nonglandular stomach, and liver. The maximum-tolerated dose is 400 mg/kg.

Target organs in rats given atorvastatin are liver, nonglandular stomach, and skeletal muscle. Minimal effects occurred after administration of 70 mg/kg for 52 weeks and no effects were observed at 5 mg/kg.

Target organs in dogs given atorvastatin are liver, gallbladder, skeletal muscle, and intestines. Minimal effects were observed after administration of 80 mg/kg for 13 weeks or 40 mg/kg for 104 weeks.

Brain and optic nerve lesions in 1 dog occurred following administration of 280 mg/kg, an intolerable dose of atorvastatin. No toxicity occurred in lens or testes.

Daily IV doses of atorvastatin up to 4 mg/kg for 2 weeks are nontoxic in rats and dogs.

Carcinogenicity:
The results of 104-week carcinogenicity studies and mice and rats yielded the following conclusions.

Atorvastatin increased the incidence of hepatocellular adenoma in male mice and hepatocellular carcinoma in female mice at 400 mg/kg.

Atorvastatin was not carcinogenic in male or female rats.

Toxicology of amorphous versus crystalline atorvastatin:
The decision to market crystalline atorvastatin resulted in additional 13-week toxicokinetic studies in mice, rats, and dogs to compare exposure and toxicity with the amorphous and crystalline forms.

The toxicities in mice and rats were not different for the amorphous versus crystalline forms.

According to initial study design, dogs were given amorphous or crystalline atorvastatin at 10, 40, or 120 mg/kg by gavage daily for 13 weeks. These doses were identical to those selected for the original 104-week toxicity study of amorphous atorvastatin in dogs.

Due to severe clinical signs, moribundity, and deaths with crystalline atorvastatin at 120 mg/kg, additional animals were given drug in an escalating-dose regimen of 80 mg/kg for 2 weeks, 100 mg/kg for 2 weeks, followed by 120 mg/kg for the remainder of the study to allow accommodation to the drug.

Severe clinical signs and death of 1 animal at 100 mg/kg resulted in discontinuation of this group in Week 4, and all surviving animals were euthanized.

No deaths occurred with amorphous atorvastatin. Two of 3 males and all 3 females given 120 mg/kg crystalline atorvastatin died or were euthanized moribund in Weeks 3, 5, or 6. In addition, a female at 40 mg/kg of crystalline was euthanized moribund during Week 8. Clinical signs in these animals included bloody diarrhea, emesis, reduced food consumption, hypoactivity, and weight loss of 19% to 27%. Emaciation, salivation, prostration, pallor, and pain when opening or palpating the mouth or tongue were also noted prior to euthanasia. In surviving animals, diarrhea and emesis were noted in all animals given 120 mg/kg of amorphous and crystalline and in females given 40 mg/kg of crystalline. No drug-related clinical signs occurred at 10 mg/kg, at 40 mg/kg of amorphous, or in males at 40 mg/kg of crystalline. The surviving male at 120 mg/kg of crystalline lost 10% of pretest body weight. Body weight and food consumption in remaining animals surviving to termination were unaffected. No drug-related changes in electrocardiographic parameters, blood pressure, or ophthalmic examinations occurred.

No alterations in hematology, urinalysis, bone marrow, or lens parameters were noted. Dose-

dependent decreases in cholesterol and phospholipids ranging from 11% to 68% occurred in all drug-treated groups. Triglycerides decreased 35% to 52% in males at 10 mg/kg of crystalline and in both sexes at 40 and 120 mg/kg of amorphous and crystalline. Alanine aminotransferase increased up to 24-fold from pretest in males at 40 mg/kg of amorphous and crystalline, and in both sexes at 120 mg/kg of amorphous and crystalline that survived to termination. Increases in ALT up to 19-fold from pretest and increases in AST, ALP, and CPK occurred in moribund animals.

Organ weights in animals surviving to termination were unaffected. Adrenal weight increased and liver and splenic weight decreased in animals euthanized moribund. Drug-related microscopic findings in dead or moribund animals included gastrointestinal congestion, adrenal cortical necrosis with congestion or hemorrhage, gallbladder mural edema with congestion and/or hemorrhage, hepatic biliary hyperplasia, and skeletal muscle degeneration. Microscopic changes in animals surviving to termination were limited to minimal to mild congestion of the gallbladder in males at 120 mg/kg and females at ≥40 mg/kg, and minimal to mild hyperplasia of the bile duct in males at ≥40 mg/kg and females at 120 mg/kg. Minimal degeneration of psoas muscle fibers in 1 male at 40 mg/kg of crystalline was noted.

Changes observed with both amorphous and crystalline atorvastatin were qualitatively similar and were consistent with changes observed previously with amorphous atorvastatin. The no-adverse-effect dose of 10 mg/kg produced similar systemic exposure with both forms of atorvastatin.

Considerable inter- and intra-animal variability in atorvastatin toxicokinetics were observed in all treated groups but no sex differences were noted (Table 4.8.1). At 10 mg/kg, Cmax and AUC(0-24) of amorphous and crystalline atorvastatin were comparable throughout the study. During the first half of the study, Cmax and AUC(0-24) at 40 and 120 mg/kg were greater in animals given crystalline compared to similar doses of amorphous. At Week 13, no major differences in Cmax and AUC(0-20) were noted between the crystalline and amorphous forms.

Conclusions:

No difference in toxicity between the amorphous and crystalline forms of atorvastatin was apparent in mice or rats.

Toxicity in dogs given crystalline drug was qualitatively similar, but more severe at doses from 40 to 120 mg/kg than that seen after doses of amorphous drug up to 120 mg/kg. Specifically, dogs given crystalline drug died or were euthanized moribund while none of the dogs given amorphous drug were as severely affected. Systemic exposure at the 40 and 120 mg/kg doses was greater in dogs given crystalline atorvastatin, perhaps explaining the differences in toxicology. The principal toxic manifestations were in the gastrointestinal tract, liver, gallbladder, and muscle. No novel organ system effects were observed with the crystalline drug form.

TABLE 4.8.1. Toxicokinetic Parameters in Dogs Given Amorphous or Crystalline Atorvastatin Orally for 6/7 or 13 Weeks[a]

Dose (mg/kg)	Cmax (ng eq/mL)					
	Amorphous			Crystalline		
	Males	Females	Combined-Sex	Males	Females	Combined-Sex
			Week 6/7			
10	74.8 ± 28.3	74.5 ± 21.4	74.7 ± 22.5	149 ± 30.0	135 ± 58.0	142 ± 42.2
40	259 ± 78.6	560 ± 781	409 ± 523	1345 ± 858	2487 ± 2472	1920 ± 1770
120	610 ± 658	1143 ± 1213	877 ± 920	14465 ± 14757[b]	3595 ± 1492[b]	9030 ± 10600[c]
			Week 13			
10	284 ± 297	75.3± 24.2	180 ± 220	145 ± 76.7	290 ± 201	217 ± 158
40	297 ± 85.6	447 ± 340	372 ± 236	1097 ± 351	774 ± 43.1[b]	968 ± 305[d]
120	2608 ± 2709	6903 ± 7102	4760 ± 5350	2640[e]	ND	2640[e]

Dose (mg/kg)	AUC(0-24) (ng eq·hr/mL)					
	Amorphous			Crystalline		
	Males	Females	Combined-Sex	Males	Females	Combined-Sex
			Week 6/7			
10	493 ± 48.0	434 ± 152	463 ± 106	476 ± 121	481 ± 140	479 ± 117
40	1343 ± 247	1253 ± 775	1300 ± 517	3573 ± 210	12847 ± 13303	8210 ± 9830
120	3990 ± 3544	4213 ± 3087	4100 ± 2970	102100 ± 88954[b]	24250 ± 9687[b]	63200 ± 68500[c]
			Week 13			
10	1480 ± 1583	312 ± 158	896 ± 1190	383 ± 212	981 ± 235	682 ± 384
40	1760 ± 1068	904 ± 652	1330 ± 920	4923 ± 2442	4840 ± 1301[b]	4890 ± 1850[d]
120	26690 ± 32803	16680 ± 16181	21700 ± 23800	16400[e]	ND	16400[e]

Reference 66

Cmax = Mean maximum plasma concentration; AUC(0-24) = Area under the plasma concentration-time curve (0-24); ND = No data available.

[a] Samples obtained predose, 1, 2, 4, 8, 12, and 24 hours postdose during Week 6 (females), Week 7 (males), and Week 13; mean ± standard deviation; analyzed by enzyme inhibition assay; N = 3, combined-sex N = 6.

[b] N = 2.

[c] N = 4.

[d] N = 5.

[e] N = 1.

Section 5
Clinical data sources

Primary development program
This NDA includes data from 31 completed clinical pharmacology studies, 21 completed clinical studies, and 2 ongoing clinical studies.

Clinical Pharmacology Studies
All told, 590 healthy males and females received atorvastatin in clinical pharmacology studies. The demographics of this population and the exposure to atorvastatin are summarized in the tables below.

TABLE 5.1. Subject Characteristics in Clinical Pharmacology Studies

Characteristic	Placebo N = 32	Atorvastatin[a] N = 590
Sex, N (%)		
Men	21 (65.6)	341 (57.8)
Women	11 (34.4)	249 (42.2)
Race, (%)		
White	28 (87.5)	532 (90.2)
Black	4 (12.5)	39 (6.6)
Asian	0 (0.0)	2 (0.3)
Other	0 (0.0)	17 (2.9)
Age, yr		
Mean	33.9	38.9
Range	19-55	18-92

[a] Includes 24 subjects with low-density lipoprotein cholesterol (LDL-C) levels between 160 and 250 mg/dL.

TABLE 5.2. Subject Exposure to Atorvastatin and Placebo

Dose (mg)	Subject-Days per Dose
0	32
0.5	68
1.0	4
2.5	98
5.0	1066
10.0	2561
20.0	1508
40.0	1271
80.0	1810
120.0	4

Clinical studies

In 21 completed clinical studies, 3522 hyperlipidemic patients participated, 2502 of them receiving at least one dose of atorvastatin. The overall demographics of the study population are summarized in the table, and this is followed by the exposure to atorvastatin by dose. Total atorvastatin exposure was 1845 patient-years with the greatest exposure at the 10 mg starting dose (1083 patient-years).

In addition to the majority of patients with Type II a and II b hyperlipidemia, the efficacy of atorvastatin was studied in a small number of patients with isolated hypertriglyceridemia (Type IV), over 300 patients with heterozygous familial hypercholesterolemia, and in about 30 patients with homozygous FH. In one study, 166 patients with NIDDM were randomized (1:1) to treatment with atorvastatin or simvastatin for 26 weeks.

TABLE 5.3. All Completed Studies Data Grouping: Patient Demographics and Baseline Characteristics

	Placebo N = 110		Atorvastatin N = 2502		Combined HMGRIs N = 742		Colestipol N = 44		Fenofibrate N = 52		Niacin N = 53		Estradiol N = 19	
Sex, N (%)														
Men	70	(64)	1386	(55)	374	(50)	24	(55)	35	(67)	35	(66)	0	(0)
Women	40	(36)	1116	(45)	368	(50)	20	(45)	17	(33)	18	(34)	19	(100)
Race, N (%)														
White	101	(92)	2346	(94)	698	(94)	38	(86)	50	(96)	49	(92)	18	(5)
Black	5	(5)	86	(3)	21	(3)	2	(5)	0	(0)	3	(6)	1	(5)
Asian	2	(2)	21	(1)	8	(1)	2	(5)	2	(4)	0	(0)	0	(0)
Other	2	(2)	49	(2)	15	(2)	2	(5)	0	(0)	1	(2)	0	(0)
Age, yr														
Median	55		57		58		58		53		56		61	
Min-Max														
Mean, SE	54, 1.1		55, 0.2		57, 0.4		57, 1.8		54, 1.2		55, 1.5		61, 1.6	
Age, N (%)														
< 70 years	104	(5)	2243	(90)	661	(89)	37	(84)	50	(96)	48	(91)	16	(84)
≥ 70 years	6	(5)	259	(10)	81	(11)	7	(16)	2	(4)	5	(9)	3	(16)
Body Mass Index, kg/m²														
Median	26		27		27		26		27		27		26	
Min-Max														
Mean, SE	26, 0.3		27, 0.1		27, 0.1		26, 0.4		27, 0.4		28, 0.4		27, 1.0	

Table 5.4. Exposure by dose in clinical studies

Dose (mg/day)	Number of patients	Exposure (patient-years)
2.5	11	1
5	49	6
10	1677	1083
20	753	301
40	493	157
60	13	2
80	383	222

As stated above, most of the exposure to atorvastatin was in the 10 mg group, in which over 750 patients were exposed for 1 year. About 100 patients were exposed to 20 mg/day for 1 year, and fewer than 50 were treated with 40 mg/day for 1 year. About half of the patients who received 80 mg/day in clinical trials received that dose for nearly one year in study 981-56, all told about 200 individuals. It is thus clear that the safety database is weighted toward the 10 mg dose of atorvastatin, which accounted for nearly 60% of the total exposure. It is also important to realize that the bulk of the exposure to both 10 and 80 mg is in patients treated for 1 year. As such, then, with regard to duration of treatment in individual patients, and adverse reactions related to cumulative exposure, these two treatment groups are better compared to one another than to the other dosage groups, where the percentage of patients receiving drug over longer periods was relatively small. Finally, for purposes of comparison, the exposure to the other HMGRIs was also in 1-year studies.

The exposure in data subgroups is discussed with the description of these subgroups in the Safety review.

An additional 751 patients received atorvastatin for the first time in ongoing extension studies as of March 15, 1996. The safety data for these and the ~1500 others continuing therapy in these studies are included in the NDA.

Comments on the adequacy of the clinical experience with atorvastatin:
Overall, the clinical experience with atorvastatin is more than sufficient to establish efficacy in lipid altering at all doses proposed for marketing. With regard to safety, while the total exposure at 80 mg was only about 20% of that at 10 mg, nevertheless, dose-related increases in certain adverse events and laboratory abnormalities were observed consistent with the experience with other members of the drug class, and thus lend some degree of assurance that there was adequate exposure at higher doses. No novel drug-induced adverse events were observed at any dose. The only exposure lacking in the original NDA submission was that to the crystalline, to-be-

marketed form of the drug. While this might, on the surface, appear as a glaring deficiency, the only possible issue raised is with regard to the safety of the 80 mg dose, which likely is characterized by a higher Cmax than that of the 80 mg amorphous form. The 4-month safety update, will, it is anticipated, fill this gap in the database as it contains comparative data on 80 mg amorphous versus crystalline atorvastatin.

Tabular summary of clinical studies:
The table that follows this section lists the 21 completed and 2 ongoing clinical trials and outlines their salient characteristics. The numbers of participants refer to the number enrolled. All told, >90% of enrolled patients completed clinical studies and efficacy and safety data are available for nearly all enrolled patients. There were no problems related to compliance and follow up in this clinical database.

Literature:
The sponsor provided copious literature pertinent to atorvastatin and to HMGRIs in general. The safety and efficacy of the class are well established over almost a decade of clinical use.

Data quality:
There are no clinical outcome data in this NDA. As such, the quality of the data included is a function of trial design and implementation, the success of follow up with regard to patient compliance, adverse event reporting, and laboratory testing for both safety and efficacy. Follow up was highly effective in the studies presented; compliance with medication was high; protocol deviations were rare; and designated central laboratories were used in the multicenter trials. No CRFs were specifically reviewed by the medical officer. Patient narratives for deaths and dropouts due to adverse events and for patients with clinically important liver function and CPK abnormalities were reviewed. Overall, the data submitted to the NDA appear to be of excellent quality.

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Table 5.5. Listing of completed and ongoing clinical studies. NDA 20-702. (6 pages)

Study Number (RR Number)	Study Design (Country)	Number of Participants		Criteria for Inclusion	Drug Administration	
					Drugs, Strengths, Dosage Form	Dosing Regimen
Completed Studies						
981-04 (720-03113)	6-week, placebo-controlled, double-blind, dose-ranging study (US and Canada)	**Total** 81 **Treatment** 69 Ator 12 Plac	**Mean Age** 53 yrs **Age Range** **Gender** 65 Men 16 Women	Patients with LDL-C >160 and <220 mg/dL and TG <300 mg/dL	Placebo capsules Atorvastatin 2.5-, 5-, 10-, 20-, and 40-mg capsules	8 weeks baseline placebo QD 6 weeks double-blind placebo or atorvastatin 2.5, 5, 10, 20, 40, or 80 mg QD
981-07 (720-03237)	12-week, open-label, 8 sequence crossover, comparative study of atorvastatin vs pravastatin and simvastatin (Germany, The Netherlands)	**Total** 92 **Treatment*** 47 Ator 21 Plac 24 Simv * 1st Phase only	**Mean Age** 59 yrs **Age Range** **Gender** 45 Men 47 Women	Patients with LDL-C >160 and <240 mg/dL and TG <300 mg/dL	Placebo tablets Atorvastatin 5- and 20-mg tablets Pravastatin 20-mg tablets Simvastatin 10-mg tablets	4 weeks baseline Placebo QD 4 weeks Period 1 Atorvastatin 5 or 20 mg QD or simvastatin 10 mg QD or pravastatin 20 mg QD 4 weeks washout Placebo QD 4 weeks: Period 2 Crossover Atorvastatin 5 or 20 mg QD or simvastatin 10 mg QD or pravastatin 20 mg QD
981-08 (720-03519)	52-week, placebo-controlled, double-blind, comparative study vs lovastatin (US)	**Total** 1049 **Treatment** 70 Plac/Ator 67 Plac/Lova 719 Ator 193 Lova	**Mean Age** 57 yrs **Age Range** **Gender** 610 Men 439 Women	Patients with LDL-C ≥160 mg/dL at Week -4 >145 mg/dL at Week -2, and ≤250 mg/dL at both Weeks -4 and -2 and TG <400 mg/dL	Placebo tablets Atorvastatin 10-mg tablets Lovastatin 20-mg tablets	6 weeks baseline Placebo QD 16 weeks double-blind Placebo, atorvastatin 10 mg, or lovastatin 20 mg QD 6 weeks atorvastatin 10 mg or lovastatin 20 mg 30 weeks atorvastatin 10 or 20 mg QD or lovastatin 20 or 40 mg QD

Study Number (RR Number)	Study Design (Country)	Number of Participants		Criteria for Inclusion	Drug Administration	
					Drugs, Strengths, Dosage Form	Dosing Regimen
Completed Studies (continued)						
981-09 (720-03594)	52-week, double-blind, comparative study of atorvastatin vs pravastatin (France, Italy, Germany, Netherlands, Spain, UK)	**Total** 305 **Treatment** 227 Ator 78 Prav	**Mean Age** 57 yrs **Age Range** **Gender** 139 Men 166 Women	Patients with LDL-C ≥ 160 mg/dL and ≤250 mg/dL and TG ≤400 mg/dL	Placebo Atorvastatin 10-mg tablet Pravastatin 20-mg tablets	6 weeks baseline Placebo QD 16 weeks double-blind 10 mg atorvastatin QD or 20 mg pravastatin QD 36 weeks double-blind 10 or 20 mg atorvastatin QD or 20 or 40 mg pravastatin QD
981-10 (720-03389)	6-month, placebo-controlled, double-blind study (US)	**Total** 39 **Treatment** 20 Ator 19 Placebo	**Mean Age** 54 **Age Range** **Gender** 22 Men 17 Women	Patients with LDL-C ≥160 and ≤250 mg/dL and TG ≤400 mg/dL	Placebo tablets Atorvastatin 10-mg tablets	6 weeks baseline Placebo QD 26 weeks double-blind Placebo or atorvastatin 10 mg QD
981-12 (720-03376)	52-week, randomized, parallel-arm study of atorvastatin and estradiol alone and in combination (US)	**Total** 86 **Treatment** 23 Plac/Stor 21 Ator 23 Ator/Estra 19 Estra	**Mean Age** 61 **Age Range** **Gender** 0 Men 86 Women	Postmenopausal, hysterectomized women with primary hyperlipidemia (LDL-C ≥160 mg/dL at Week -2 and >145 mg/dL at Week -1) and TG ≤400 mg/dL	Placebo tablets Atorvastatin 10-mg tablets 17β-Estradiol 1 mg tablet	6 weeks baseline Placebo QD 12 weeks double-blind 10 mg atorvastatin QD or placebo QD or 1 mg estradiol QD or 10 mg atorvastatin and 1 mg estradiol QD 40 weeks 10 mg atorvastatin QD or 1 mg estradiol QD or 10 mg atorvastatin and 1 mg estradiol QD
981-13 (720-03595)	4-week, open-label, comparative study of atorvastatin with simvastatin (Australia)	**Total** 25 **Treatment** 13 Ator 12 Simv	**Mean Age** 61 yrs **Age Range** **Gender** 13 Men 12 Women	Patients with NIDDM and LDL-C ≥160 mg/dL	Atorvastatin 10-mg tablets Simvastatin 10-mg tablets	4 weeks, open-label 10 mg atorvastatin QD or 10 mg simvastatin QD

Study Number (RR Number)	Study Design (Country)	Number of Participants	Criteria for Inclusion	Drug Administration	
				Drugs, Strengths, Dosage Form	Dosing Regimen

Completed Studies (continued)						
981-14 (720-03596)	4-week, open-label, parallel comparative study of atorvastatin and simvastatin (UK)	**Total** 22 **Treatment** 11 Ator 11 Simv	**Mean Age** 54 yrs **Age Range** **Gender** 9 Men 13 Women	Patients with LDL-C >4.0 mmol/L and TG <4.0 mmol/L	Placebo Atorvastatin 10-mg tablets Simvastatin 10-mg tablets	6 weeks baseline Placebo QD 4 weeks open-label 10 mg atorvastatin or 10 mg simvastatin QD
981-25 (720-03369)	4-month, placebo-controlled, double-blind, dose-ranging study (US)	**Total** 228 **Treatment** 172 Ator 56 Plac	**Mean Age** 56 yrs **Age Range** **Gender** 142 Men 86 Women	Patients with LDL-C ≥160 and ≤250 mg/dL and TG ≤400 mg/dL	Placebo capsules Atorvastatin 10- and 20-mg capsules	6 weeks baseline Placebo QD 16 weeks double-blind Placebo or atorvastatin 10, 40, or 80 mg QD
981-37 (720-03598)	52-week, double-blind, parallel group, comparative study of atorvastatin with simvastatin (Australia)	**Total** 177 **Treatment** 132 Ator 45 Simv	**Mean Age** 57 yrs **Age Range** **Gender** 94 Men 83 Women	Patients with LDL ≤300 mg/dL at Weeks -4 and -2, and ≥160 mg/dL at Week -4, and ≤145 mg/dL at Week -2 (lower value within 20% of higher value). TG ≤400 mg/dL	Placebo tablets (atorvastatin) capsules (simvastatin) Atorvastatin 10-mg tablet Simvastatin 10-mg capsule	6 week baseline Placebo QD 16 weeks double-blind 10 mg atorvastatin QD or 10 mg simvastatin QD 36 weeks double-blind 10 or 20 mg atorvastatin QD 10 or 20 mg simvastatin QD
981-38 (720-03335)	4-week, placebo-controlled, dose-ranging study (US and Canada)	**Total** 56 **Treatment** 42 Ator 14 Plac	**Mean Age** 51 yrs **Age Range** **Gender** 48 Men 8 Women	Patients with plasma TG ≥350 mg/dL	Placebo tablets Atorvastatin 5-, 10-, and 40-mg tablets	4 weeks baseline Placebo QD 4 weeks double-blind 5, 20, or 80 mg atorvastatin QD or placebo
981-42 (720-03557)	12-week, open-label, comparative study vs niacin (US)	**Total** 108 **Treatment** 55 Ator 53 Niacin	**Mean Age** 55 **Age Range** **Gender** 70 Men 38 Women	Patients with TC ≥200 mg/dL, TG ≥200 mg/dL and ≤800 mg/dL, and apo B ≥110 mg/dL	Atorvastatin 10-mg tablets Niacin (immediate-release) 100-, 250-, and 500-mg tablets	6 weeks baseline Placebo 12 weeks open-label 10 mg atorvastatin QD or 1 g niacin TID

Study Number (RR Number)	Study Design (Country)	Number of Participants	Criteria for Inclusion	Drug Administration	
				Drugs, Strengths, Dosage Form	Dosing Regimen
Completed Studies (continued)					

981-43 (720-03361)	12-week, open-label, comparative study of atorvastatin vs colestipol and in combination with colestipol (US and Canada)	**Total** 106 **Treatment** 42 Ator 20 Ator/Cole 44 Cole	**Mean Age** 55 **Age Range** **Gender** 58 Men 48 Women	Patients with LDL-C >160 mg/dL and TG <350 mg/dL	Atorvastatin 10-mg tablets Colestipol 5-g granule packets	12 weeks (1) atorvastatin 10 mg QD or (2) colestipol 5 g BID for 2 weeks increased to 10 g BID for remaining 10 weeks or (3) combination atorvastatin 10 mg QD and colestipol 5 g BID for 2 weeks increasing to 10 g BID for remaining 10 weeks
981-44 (720-03525)	6-week randomized, parallel group open-label study (South Africa)	**Total** 22 **Treatment** 22 Ator	**Mean Age** 38 yrs **Age Range** **Gender** 6 Men 16 Women	Patients with LDL-C >250 mg/dL and TG <400 mg/dL and tendon xanthomata or genetically defined heterozygous familial hypercholesterolemia	Placebo tablets Atorvastatin 10-mg tablets	4 weeks baseline Placebo 6 weeks open-label 40 mg atorvastatin BID or 80 mg atorvastatin QD
981-47 (720-03490)	26-week, randomized double-blind parallel group comparative study with simvastatin (US)	**Total** 166 **Treatment** 84 Ator 82 Simv	**Mean Age** 61 yrs **Age Range** **Gender** 63 Men 103 Women	Patients with NIDDM and LDL-C ≥130 mg/dL and TG ≥150 and ≤600 mg/dL	Placebo tablets Atorvastatin 10-mg tablets Simvastatin 10-mg tablets	6 weeks baseline Placebo QD 4 weeks double-blind 10 mg atorvastatin QD or 10 mg simvastatin QD 22 weeks double-blind 10 or 20 mg atorvastatin QD or 10 or 20 mg simvastatin QD
981-48 (720-03599)	12-week open-label study (US)	**Total** 22 **Treatment** 22 Ator	**Mean Age** 48 yrs **Age Range** **Gender** 22 Men 0 Women	Patients with Type IIa (LDL-C ≥160 mg/dL and TG <200 mg/dL), Type IIb (LDL-C ≥160 mg/dL, TG ≥200 mg/dL and <650 mg/dL), or Type IV (LDL-C <160 mg/dL, TG >300 mg/dL and <650 mg/dL) dyslipidemias	Placebo tablets Atorvastatin 20- and 40-mg tablets	6 weeks baseline Placebo QD 12 weeks open-label 80 mg atorvastatin QD

Study Number (RR Number)	Study Design (Country)	Number of Participants	Criteria for Inclusion	Drug Administration	
				Drugs, Strengths, Dosage Form	Dosing Regimen

Completed Studies (continued)

981-54 (720-03702)	8-week open-label study (South Africa)	**Total** 8 **Treatment** 8 Ator	**Mean Age** 22 yrs **Age Range** **Gender** 5 Men 3 Women	Patients with documented homozygous FH	Placebo tablets Atorvastatin 40-mg tablets	8 weeks baseline Placebo QD 8 weeks open-label 80 mg atorvastatin QD
981-55 (720-03560)	24-week comparative study vs fenofibrate (Canada)	**Total** 99 **Treatment** 47 Ator 52 Feno	**Mean Age** 52 yrs **Age Range** **Gender** 68 Men 31 Women	Patients with plasma total cholesterol ≥200 mg/dL; TG ≥200 and <800 mg/dL, and apo B ≥110 mg/dL	Atorvastatin 10-mg tablets Fenofibrate 100-mg tablets	12 weeks open-label 10 mg atorvastatin QD or 100 mg fenofibrate TID 12 weeks open-label 20 mg atorvastatin QD or 100 mg fenofibrate TID
981-56 (720-03600)	52-week, open-label, comparative study of atorvastatin vs colestipol alone, and vs colestipol/ atorvastatin combination, and colestipol/simvast atin combination (US and Canada)	**Total** 469 **Treatment** 199 Ator 134 Cole/Ato r 136 Cole/Sim	**Mean Age** 48 **Age Range** **Gender** 258 Men 211 Women	Patients with heterozygous FH and LDL-C >220 mg/dL and <400 mg/dL and TG <400 mg/dL	Atorvastatin 10- and 40-mg tablets Simvastatin 20-mg tablets Colestipol 5-g packets	4 weeks double-blind 40 mg atorvastatin QD or 5 g colestipol BID 12 weeks double-blind 80 mg atorvastatin QD or 10 g colestipol BID 4 weeks double-blind 80 mg atorvastatin QD, or 20 mg atorvastatin QD and 10 g colestipol BID, or 20 mg simvastatin QD and 10 g colestipol BID 32 weeks 80 mg atorvastatin QD, or 40 mg atorvastatin QD and 10 g colestipol BID, or 40 mg simvastatin QD and 10 g colestipol BID

Study Number (RR Number)	Study Design (Country)	Number of Participants	Criteria for Inclusion	Drug Administration	
				Drugs, Strengths, Dosage Form	Dosing Regimen
Completed Studies (continued)					

981-57 (720-03500)	52-week, double-blind, comparative study atorvastatin vs pravastatin (Germany, Netherlands)	**Total** 297 **Treatment** 224 Ator 73 Prav	**Mean Age** 59 yrs **Age Range** **Gender** 165 Men 132 Women	Patients with LDL-C > 160 mg/dL and ≤250 mg/dL TG < 400 mg/dL	Atorvastatin 10- and 40-mg tablets Pravastatin 20-mg tablets	6 weeks baseline Placebo QD 8 weeks double-blind 10 or 20 mg atorvastatin QD or 20 or 40 mg pravastatin QD 8 weeks double-blind 10, 20, or 40 mg atorvastatin QD or 20 or 40 mg pravastatin QD 36 weeks double-blind 10, 20, 40, or 80 mg atorvastatin QD or 20 or 40 mg pravastatin QD
981-96 (720-03602)	6-week, placebo-controlled, nonblind, dose-ranging study (US)	**Total** 65 **Treatment** 56 Ator 9 Plac	**Mean Age** 58 yrs **Age Range** **Gender** 22 Men 43 Women	Patients with LDL-C ≥160 mg/dL and ≤250 mg/dL and TG ≤400 mg/dL	Placebo tablets Atorvastatin (crystalline) 10- and 20-mg tablets	6 weeks baseline Placebo QD 6 weeks nonblind Placebo or atorvastatin 10, 20, 40, 60, or 80 mg QD
Ongoing Studies						
981-76	20-week, randomized, open-label, crossover study comparing atorvastatin with simvastatin (Scotland)	**Total** **Treatment**	**Mean Age** **Age Range** **Gender** Men Women	Patients with total cholesterol ≥6.0 and ≤9.0 mmol/L, and TG ≥2.0 and ≤4.0 mmol/L	Atorvastatin 10-mg tablets Simvastatin 10-mg tablets	6-week baseline 8-10 weeks double-blind Atorvastatin 40 mg QD Simvastatin 40 mg QD 8-10 weeks double-blind Atorvastatin 40 mg QD Simvastatin 40 mg QD
981-80	Open-label, uncontrolled, compassionate-use study (Worldwide)	**Total** 51 **Treatment** 51 Ator	**Mean Age** **Age Range** **Gender** Men Women	Patients with confirmed homozygous familial hypercholesterolemia or severe hypercholesterolemia refractory to conventional therapy	Atorvastatin 10-, 20-, and 40-mg tablets	4 weeks open-label 40 mg atorvastatin QD Remainder of study 80 mg atorvastatin QD or highest tolerated dose

Section 6
Human pharmacokinetics and bioavailability

Atorvastatin has multiple amorphous and crystalline forms. Originally, bulk drug substance was amorphous; most of the clinical pharmacology studies were conducted with tablets prepared from this material. Midway through the clinical pharmacology program, newly prepared bulk drug substance assumed a more stable crystalline form. A bioavailability study showed that the rate, but not the extent, of atorvastatin absorption was significantly higher (23% increase in Cmax) following administration of tablets prepared from the crystalline bulk drug. As a result, dose-proportionality and food-effect studies that had previously been conducted with tablets prepared from amorphous B bulk drug were repeated with tablets prepared from crystalline bulk drug.

6.1 Absorption
Atorvastatin was rapidly absorbed after oral administration; maximal plasma concentrations occurred within 1 to 4 hours. Mean Cmax and AUC values following multiple-dose administration (2 weeks) were generally greater than the corresponding single-dose values. Plasma atorvastatin concentrations reached steady state by the third day of dosing with both once- and twice-daily dosing.

Atorvastatin tablets were fully bioavailable (95%-99%) compared with solution.
The absolute bioavailability of atorvastatin (parent drug) was approximately 12%, and the systemic availability of HMG-CoA reductase inhibitory activity was approximately 30%. Atorvastatin's low systemic availability was attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

Mean atorvastatin equivalent Cmax values were higher in female (18%) and elderly (43%) subjects compared with male and young subjects, respectively. Mean atorvastatin equivalent AUC values were higher (27%) in elderly than young subjects and slightly lower (11%) in female than male subjects. Thus, modest age- and gender-related differences in atorvastatin-equivalent pharmacokinetics are observed.

There was considerable inter- and intrasubject variability in atorvastatin pharmacokinetics.

Food decreased the rate of atorvastatin-equivalent absorption by approximately 25%, while the extent of atorvastatin-equivalent absorption was minimally decreased; mean AUC(0-24) was only 9% lower following administration with the evening meal compared with administration 3 hours after the meal. Atorvastatin pharmacodynamics were similar following drug administration in the evening with meals or after meals. Mean reductions from baseline for both treatments were 24% for total cholesterol and 40% for LDL-cholesterol. The impact of food on rate and extent of atorvastatin absorption, as well as lipid-lowering effects, was similar for both amorphous B and crystalline I drug formulations.

The effect of morning-versus-evening dosing on pharmacokinetic and pharmacologic activity was assessed. Mean Cmax was 31% lower, mean tmax was 57% later, and AUC(0-24) was 29% lower following administration of atorvastatin in the evening, when compared with corresponding values obtained following dosing in the morning. Mean LDL-cholesterol reductions from baseline (48%) were not influenced by time of day of administration. Thus, rate and extent of atorvastatin-equivalent absorption are lower during evening administration compared with morning administration. However, these differences do not affect pharmacologic

activity.

6.2 Distribution
Mean apparent volume of distribution of atorvastatin (parent drug) was extensive, approximately 565 L, and was thus much greater than total body water (~40 L). Atorvastatin was 98% or more bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicated poor drug penetration into red blood cells.

6.3 Metabolism
In vitro metabolism of atorvastatin was studied in human hepatic microsomes. Two metabolites, ortho- and parahydroxy atorvastatin, were formed. In studies with human intestinal microsomes, atorvastatin was biotransformed to these same 2 metabolites, suggesting presystemic metabolism of atorvastatin. An additional metabolite, a beta-oxidized product, was produced following incubation of atorvastatin in freshly isolated human hepatocyte suspensions. In addition, studies using microsomal preparations containing expressed human cytochrome P450 enzymes (CYP1A1, 1A2, 2A6, 2B6, 2D6, 2E1, or 3A4) showed that only CYP3A4 was able to metabolize atorvastatin, resulting in formation of ortho- and parahydroxy atorvastatin. This finding is consistent with increased plasma concentrations of atorvastatin observed in humans following coadministration of atorvastatin with erythromycin, a known inhibitor of CYP3A4.

In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites was similar to that of atorvastatin. In humans, mean atorvastatin elimination t½ was approximately 14 hours, but the half-life of HMG-CoA reductase inhibitory activity was longer (approximately 20 to 30 hours) due to the contribution of longer-lived active metabolites. There was no indication of dose dependence in the fraction of absorbed atorvastatin appearing as active metabolites. Atorvastatin represents as much as 60% of circulating HMG-CoA reductase inhibitory activity during early absorption and approximately 30% for the rest of the 24-hour dosing interval.

To assess the mass balance and metabolic profile of atorvastatin, 6 subjects were given single daily 20-mg doses of unlabeled atorvastatin for 2 weeks followed by a single 20-mg (105.4 μCi) dose of [14 C]atorvastatin. Plasma radioactivity (t½, 62.5 hr) was detectable longer than atorvastatin-equivalent concentrations (t½, 12.6 hr), suggesting that there were relatively long-lived metabolites in plasma that do not inhibit HMG-CoA reductase.

Mean elimination t½ values following single doses were similar to those after multiple doses.

6.4 Excretion
In humans, atorvastatin and/or metabolites are probably eliminated in bile following hepatic and/or extrahepatic metabolism. However, the drug does not appear to undergo significant enterohepatic recirculation. Mean total recovery in urine and feces collected for 96 hours postdose was approximately 1.2% and 89.4% of dose, respectively. Recovery of less than 2% of an atorvastatin dose in urine following oral administration suggests that the kidneys play a minor role in elimination.

6.5 Bioequivalence
Extent, but not rate, of absorption (mean Cmax values approximately 30% higher) for 10- and 40-mg market-image tablets prepared from crystalline I drug substance was equivalent to those of 10- and 40-mg clinical trial tablets prepared from amorphous B drug substance. Rate and

extent of absorption for 10- and 40-mg market-image tablets (crystalline I bulk drug) manufactured in Freiburg, Germany were bioequivalent to 10- and 40-mg market-image tablets (crystalline I bulk drug) prepared in Lititz, Pennsylvania.

6.6 Drug Interaction

Studies were done to investigate interactions between atorvastatin and drugs that are cytochrome P450 substrates or inhibitors (antipyrine, erythromycin, ethinyl-estradiol, cimetidine), drugs with narrow therapeutic indices (digoxin, warfarin), and drugs that may inhibit atorvastatin absorption (antacids, colestipol). The effects of atorvastatin on antipyrine, digoxin, ethinyl estradiol, and norethindrone pharmacokinetics, as well as warfarin pharmacodynamics, were evaluated. In addition, the effects of Maalox TC, cimetidine, and erythromycin on atorvastatin pharmacokinetics were evaluated. The effects of Maalox® TC, cimetidine, and colestipol on atorvastatin pharmacodynamics were also evaluated.

Seven drug interaction studies were conducted in healthy subjects. In addition, an interaction with colestipol was evaluated in a Phase 3 study in patients with hyperlipidemia.

Antipyrine

Coadministration with atorvastatin had no effect on antipyrine pharmacokinetics. Atorvastatin has no substantial effect on absorption or clearance of antipyrine, and does not affect oxidative pathways that metabolize antipyrine.

Digoxin

Coadministration of atorvastatin and digoxin increased steady-state plasma digoxin concentrations by approximately 20%, compared with those measured following digoxin alone. This was probably due to an increase in extent of digoxin absorption, rather than a decrease in digoxin clearance. Patients taking digoxin should be monitored appropriately when atorvastatin therapy is initiated.

Oral Contraceptives

Subjects received Ortho-Novum 1/35 QD alone (for 21 days during the first and second of 3 sequential menstrual cycles) and in combination with atorvastatin (40 mg QD for 22 days) (for 21 days during the third of 3 sequential menstrual cycles) (Study 981-66). (20) Following coadministration with atorvastatin, mean steady-state ethinyl estradiol and norethindrone Cmax values were 25% to 30% higher than the respective Cmax values following Ortho-Novum alone. Similarly, ethinyl estradiol and norethindrone AUC(0-24) values were 20% to 30% higher than the respective AUC(0-24) values following Ortho-Novum alone. Mean ethinyl estradiol t½ values were similar (~17 hr) for both treatment groups, suggesting no change in ethinyl estradiol systemic clearance. Mean norethindrone t½ value increased slightly (from 12 to 13 hr) when Ortho-Novum was administered with atorvastatin. Both ethinyl estradiol and norethindrone undergo first-pass metabolism, (45,46) with a loss of approximately 40% of dose. Increases in ethinyl estradiol and norethindrone concentrations in the presence of atorvastatin are probably due to a decrease in first-pass metabolism. Thus, because ethinyl estradiol and norethindrone concentrations increase when atorvastatin is administered with birth-control pills, contraceptive failure due to a drug-drug interaction is not expected. However, increased ethinyl estradiol concentrations should be considered when selecting oral contraceptive doses.

Warfarin

In 12 patients receiving stable, chronic warfarin therapy, administration of atorvastatin (80 mg QD) for 15 days had no consistent effect on the anticoagulant action of warfarin. Mean

prothrombin time decreased minimally during the first 4 days of atorvastatin dosing, and returned to normal by the end of the dosing period. The transient decrease of 1.7 ± 0.4 (mean ± SE) seconds was not felt to be clinically important. With lovastatin, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients.

Maalox TC
The coadministration of atorvastatin and Maalox TC decrease rate and extent of atorvastatin absorption at steady-state, though LDL-cholesterol reduction is unaffected.

Cimetidine
Coadministration of atorvastatin and cimetidine did not alter the rate or extent of atorvastatin absorption, nor did cimetidine alter LDL-cholesterol reduction.

Erythromycin
Coadministration of atorvastatin and erythromycin resulted in higher plasma atorvastatin-equivalent concentrations than following administration of atorvastatin alone. Mean atorvastatin-equivalent Cmax and AUC values following administration of atorvastatin with erythromycin were 38% and 33%, respectively, higher than those following administration of atorvastatin alone.

Colestipol
In patients receiving 40 mg atorvastatin, coadministration of colestipol reduced the 8- to 16-hour postdose atorvastatin-equivalent concentration by approximately 26%. There was an additive LDL-C reduction following administration of atorvastatin and colestipol together compared with either drug alone.

6.7 Special Populations
Formal Studies
Age and Gender
As mentioned earlier, modest age- and gender-related differences in atorvastatin-equivalent pharmacokinetics are observed, with mean atorvastatin equivalent AUC values were higher (27%) in elderly than young subjects and slightly lower (11%) in female than male subjects.

Renal Insufficiency
Renal impairment had negligible effects on the lipid-lowering effects and pharmacokinetic behavior of atorvastatin and its active metabolites. Thus, dose adjustments in patients with mild renal dysfunction are not necessary.

Hepatic Insufficiency
Plasma atorvastatin-equivalent concentrations and extent of atorvastatin-equivalent absorption were markedly elevated (approximately 16-fold in Cmax and 11-fold in AUC) in Child-Pugh B patients compared to those in healthy subjects. However, there was no difference in terminal elimination half-lives between patients with hepatic insufficiency and healthy subjects. Atorvastatin pharmacokinetic results were similar to those of pravastatin and fluvastatin in patients with liver dysfunction (i.e., AUC and Cmax values increased with little change in elimination t½). These changes are consistent with marked reduction in hepatic first-pass metabolism. Lipid responses were similar for healthy subjects and patients with hepatic impairment. Because of markedly increased plasma concentrations, it is recommended that

atorvastatin not be used in patients with advanced liver disease.

Nonformal Analyses
Race
A formal study was not done to characterize potential race-dependent pharmacokinetic behavior. However, no difference in AUC values in black and white subjects was seen in an analysis of the distribution of normalized atorvastatin-equivalent AUC values from black and white subjects who participated in clinical pharmacology studies.

Subjects With Elevated LDL-C Levels
Based on similar AUC values, subjects with elevated LDL-C levels have similar atorvastatin exposure compared with normocholesterolemic subjects.

6.8 Pharmacokinetic/Pharmacodynamic Assessment
The atorvastatin pharmacokinetic-pharmacodynamic relationship was assessed following administration of 5, 20, and 80 mg atorvastatin QD for 6 weeks to subjects with LDL-cholesterol levels between 160 and 250 mg/dL. The relationship between percent change in LDL-cholesterol and atorvastatin dose appeared log-linear. Drug dose rather than systemic drug concentration correlates with LDL-cholesterol reduction. Individualization of drug dosage should therefore be based on therapeutic response.

Conclusions
The results presented here characterize the absorption, distribution, metabolism, and excretion of atorvastatin, support a QD dosing regimen, and suggest dose adjustments appropriate for different patient populations or patients receiving concurrent medications. The pharmacokinetic non-bioequivalence of the amorphous and crystalline tablets appears based upon a more rapid absorption of the crystalline drug. The extent of absorption is the same for both forms. The review of clinical safety will address whether the increased Cmax has any apparent implications for patients.

Section 7
Efficacy review

Introduction to the review of clinical efficacy

The clinical data submitted in support of NDA 20-702 (Atorvastatin calcium tablets) are derived from 21 completed trials, as well as from 2 ongoing studies, one on the mechanism of action of the drug and the second an open-label extension study in the treatment of refractory hypercholesterolemia and homozygous FH.

Organization:

The review of the clinical efficacy data will be divided into several sections, for the most part focused on the trial or trials that support specific efficacy claims made in the package insert. Those sections are as follows:

- 7.1) placebo controlled studies of the efficacy of atorvastatin in Types II a and II b hyperlipoproteinemia
- 7.2) studies comparing the efficacy of atorvastatin to that of other HMGRIs in Types II a and II b hyperlipoproteinemia
- 7.3) studies comparing the efficacy of atorvastatin to that of placebo and to that of niacin and fenofibrate in hypertriglyceridemic patients
- 7.4) studies in patients with severe hypercholesterolemia, predominantly heterozygous FH
- 7.5) studies in the treatment of FH homozygotes
- 7.6) atorvastatin in NIDDM and postmenopausal females
- 7.7) atorvastatin effects on hemorrheology
- 7.8) efficacy of atorvastatin in subsets of the pooled study population

This last section summarizes the sponsor's analyses of efficacy data pooled from all patients in completed parallel-group studies (i.e., every study except 981-07, a crossover study). The final measurement in each study prior to dose titration (i.e., fixed-dose treatment phase; Week 16 for Study 981-56) was used for analysis. Only patients who received atorvastatin monotherapy were included (i.e., patients receiving atorvastatin plus colestipol or atorvastatin plus estradiol were excluded). Data from patients with Types IIa and IIb hypercholesterolemia were kept separate from those with Type IV hyperlipidemia.

The data for patients who received 10 mg of atorvastatin were summarized to evaluate the effects of age (<70 years versus >70 years), gender, menopausal status for women (indicated on medical history case report forms or when not indicated, defined by age category >50 years versus <50 years), race (white versus nonwhite), NIDDM (presence or absence based on study entry criteria, concurrent medications, or glucose >160 mg/dL), and hypertension (presence or absence based on concurrent medications).

In each section, the general structure of the individual or grouped trials will be reviewed in tabular or text format. Following this will be a discussion of the important efficacy outcomes of each study or group of studies with tables and graphics as required for clarification. Salient features of the results as timing and durability of response, and apparent dose dependence will be discussed. Finally, the efficacy results supporting claims in the proposed label for atorvastatin will be so identified, and comments offered on the appropriateness of those claims.

The sections outlined above will emphasize the data demonstrating efficacy, and will address specific safety issues only as they pertain to the population or endpoints being studied. Overall safety of the drug across doses and in comparison to other HMGRIs studied will be covered in the review of safety in a different section of the NDA review (section 8).

In the interest of space and ease in utilizing this review, as the methodology of the clinical studies in this NDA was generally shared throughout, this will be described below. Unique or important aspects of design, implementation, inclusion, exclusion criteria, and endpoint parameters will be clarified in the summary of individual studies.

General methods:

Inclusion criteria:

These varied from study to study, most prominently in the lipid parameters required for entry and are indicated in the sections covering the individual studies. Most studies, unless otherwise stated, were conducted in patients with varied hyperlipidemia types, including primary hypercholesterolemia (LDL-C >135 mg/dL and TG <200 mg/dL), mixed dyslipidemia (LDL-C >135 mg/dL and TG >200 mg/dL), and isolated hypertriglyceridemia (LDL-C <135 mg/dL and TG >200 mg/dL). Several studies were designed to select for a sample of patients with a specific type of hyperlipidemia. Specifically, Study 981-054, an 8-week, uncontrolled study, was conducted in patients with documented homozygous FH and ongoing Study 981-080 in patients with confirmed homozygous FH or patients with other insufficiently controlled hypercholesterolemia. Study 981-044 (6 weeks) and Study 981-056 (52 weeks) were cor ducted in patients with severe hypercholesterolemia, either heterozygous FH or non-FH. Studies 981-038, 981-042, and 981-055 were conducted in patients with hypertriglyceridemia. Studies 981-013 and 981-047 were conducted in patients with noninsulin dependent diabetes mellitus (NIDDM) as determined by criteria of the National Diabetes Data Group in the United States. Study 981-012 was conducted in postmenopausal women.

Exclusion criteria:

Patients generally were excluded from study entry if they were pregnant or nursing, or if they had active liver disease or hepatic dysfunction, defined as aspartate amino transferase (AST) or alanine amino transferase (ALT) ranging from 1.5 times the upper limit of normal (ULN) to >3.0 × ULN depending on the nature of the study and possible risk-benefit relationship. Renal dysfunction, nephrotic syndrome, dysproteinemias, uncontrolled hypertension, or diabetes mellitus and/or other metabolic or endocrine disease known to influence serum lipids or lipoproteins excluded patients from most studies. Patients with current or recent histories of substance abuse or who consumed an above-average number of alcoholic drinks per week (the actual values varied by geographical region) were excluded. Patients taking prohibited concurrent medications such as lipid-regulating agents including niacin, probucol, Metamucil® (>2 tbsp/day), fibrates and derivatives, bile acid sequestering resins, other HMG-CoA reductase inhibitors (HMGRIs), and fish oils were excluded from entering the studies. Patients were also instructed not to take any of these medications (unless it was their study treatment) during the study. Some studies excluded patients with a history of myocardial infarction, coronary angioplasty, coronary artery bypass graft, or severe or unstable angina pectoris within the 3 months before study entry. Patients could not be receiving active medication in another clinical

study concurrently or within 30 days of screening except for atorvastatin extension studies. Twenty-two patients from Phase 2 studies were allowed to participate immediately in screening for a Phase 3 study.

Diet:

For all studies, at entry into the baseline period, patients were counseled on following the National Institutes of Health (NIH) National Cholesterol Education Program (NCEP) Step 1 Diet, which limited dietary cholesterol to <300 mg/day, saturated fats to <10% of total calories, and total fats to <30% of total calories; or a similar diet. Dietary adherence was monitored by diaries completed during the last week of the dietary baseline phase, at protocol-specified interval(s) during the study, and at the end of the study. Patients were not randomized if they could not maintain an adequate diet during baseline, based on review of diary information. Studies in Europe applied a Food Frequency Questionnaire (FFQ) to assess overall dietary compliance as well as 24-hour dietary recall information to monitor adherence to the Step 1 diet. In all studies, adherence to diet was within expectations for this patient population and considered adequate to evaluate efficacy of drug treatment.

Treatments protocols:
At the end of the baseline period, eligible patients were randomly assigned to treatment and were counseled to maintain their diet for the duration of active treatment. Active treatment phases ranged from 4 to 52 weeks, and doses of atorvastatin used ranged from 2.5 to 80 mg.

In Studies 981-004, 981-010, 981-013, 981-014, 981-038, 981-042, 981-044, 981-048, and 981-054, patients received a fixed- or single-dose level or treatment throughout the study.

In Studies 981-008, 981-009, 981-012, 981-037,981-043, 981-047, 981-055, 981-056, and 981-057, patients received a fixed-dose or treatment during the first 4 to 16 weeks of the study, followed by a dose-titration or treatment-change in which the dose of study medication was doubled or treatment was changed from placebo to active treatment, or from treatment with one active agent to combination treatment.

Study 981-007 was a 2-period, crossover design comprising 4-week treatment arms separated by a 4-week wash out period.

Studies 981-008, 981-009, 981-012, 981-037, and 981-057 were designed to provide long-term (1 year) safety information and supportive proof of efficacy. In addition, these studies compared the effects of atorvastatin with lovastatin, pravastatin, simvastatin, or estradiol.

Dosing and Lipid Measurements

Patients were instructed to take study medication with the evening meal. Only Study 981-44 used anything other than once-daily dosing (compared 40 BID to 80 QD). At all clinic visits, fasting blood samples for lipid profile were drawn between 6 and 18 hours postdose. If a patient could not keep the visit or could not adhere to the 12-hour fast (water allowed) prior to the blood draw, the visit was rescheduled within 3 days. Certified central laboratories were used in all 17 multicenter studies.

Efficacy parameters and statistical methods
Statistical Methodology

Evaluability of Data
Patients' data were included in an analysis if they had baseline data for the parameter of interest and at least 1 follow-up measurement collected within 3 days of last receiving treatment. The last treatment-phase observation was carried forward (LOCF) for patients without a measurement at the time point of interest. In studies with more than 1 treatment period, data were not carried forward or backward from 1 period to another. Protocol variations were not used to exclude patients' data from any analyses.

Three studies each had data excluded from an entire center. All efficacy data from Center 002, Study 981-07 were excluded due to problems noted at an internal audit. All efficacy data from Center 10, Study 981-25 were excluded due to inconsistencies noted in the diet diary data. All laboratory data from Center 005, Study 981-57 were excluded due to a mishandling of laboratory samples. These instances were communicated to the FDA and documented in the research reports.

The percentage of randomized patients in an individual study included in an analysis of the percent change from baseline in LDL-C ranged from 85% in Study 981-07 to 100% in Studies 981-13, 981-37, 981-44, 981-48, 981-54, and 981-96.

Lipid Values
Primary parameters of efficacy were the percent change from baseline in LDL-C (and rarely apo B) at the final time point in each study prior to any scheduled dose titration, except for Studies 981-56 and 981-57. (In Study 981-56 there was a forced titration from 40 to 80 mg at Week 4 for all patients in the atorvastatin monotherapy treatment group, so the Week 16 time point was used. In Study 981-57 there were multiple possible dose titrations and Week 52 was the primary time point.) Secondary efficacy parameters include the percent changes from baseline in total cholesterol, TG, HDL-C, VLDL-C, the non-HDL-C/HDL-C ratio, and the apo B/ HDL-C ratio at prespecified time points. Many studies also collected data on apo A-I and Lp(a), and some studies collected additional lipid and lipoprotein parameters.

The baseline for each parameter was clearly defined in the individual protocols. In most protocols, lipids were collected 2 or 3 times between Weeks -2 and 0 and the mean of those measurements was used as the baseline.

The Friedewald formula (LDL-C = Total cholesterol - [HDL-C + TG/5]) was used to estimate LDL-C except in studies evaluating patients with isolated hypertriglyceridemia (Studies 981-38, 981-42, and 981-55) and in cases of mixed lipidemia where the triglyceride level was >400 mg/dL. In most cases where the Friedewald formula was not used, LDL-C was measured directly using the beta-Quant method. If the beta-Quant values were not available, LDL-C was calculated using the DeLong Formula (LDL-C = Total cholesterol - [HDL-C + TG/6]) to correct for hypertriglyceridemia.

The definition of Fredrickson Types used in the efficacy review is seen in the listing below. These are the definitions used by the sponsor in the analysis of response by lipid phenotype, which will be reviewed here as well.

Fredrickson type	Descriptive name	lipid criteria
II a	primary hypercholesterolemia	LDL-C ≥135, TG <200
II b	combined hyperlipidemia	LDL-C ≥135, TG ≥200
IV	isolated hypertriglyceridemia	LDL-C <135, TG ≥200

Statistical Analyses

The percent changes from baseline lipid and lipoprotein parameters in the individual studies were evaluated using analysis of covariance (ANCOVA). The primary model included the effects of treatment and center, for multicenter studies, and the baseline level as a covariate. Studies 981-04, 981-38, and 981-43 did not include the baseline covariate, while others included additional stratification variables. Adjusted means for the percent changes from baseline were the least squares means based on the primary model and are the values presented by the sponsor in the individual study reports. All testing was 2-sided and conducted at the 5% level of significance. In general, the adjusted means were minimally different from unadjusted means and will be utilized in this review.

7.1 Efficacy of atorvastatin in moderate primary hypercholesterolemia

Introduction

The placebo-controlled studies outlined in the table below are reviewed together as the results demonstrate the consistency of the effect of atorvastatin on plasma lipids in patients with moderate hypercholesterolemia. Note that the inclusion criteria for these trials results in the enrollment of patients with both Fredrickson type IIa (LDL-C ≥135, TG <200)and IIb (LDL-C ≥135, TG >200) hyperlipoproteinemia.

Table 7.1.1. Atorvastatin in moderate hypercholesterolemia: Placebo-controlled studies

Study #	General design	Enrollment	Age/gender	Lipid inclusion	Baseline lipids	Dose regimen
981-04	6-week, pl. controlled, 2X blind, dose-ranging; amorphous atorvastatin	69 atorv 12 placebo	mean 53 yrs 45 men 47 women	LDL-C >160 and <220, TG <300	Pl At LDL 185 189 TG 170 180	8 weeks placebo run-in, 6 weeks pl, atorv 2.5, 5, 10, 20, 40, 80 mg QD
981-96	6-week, pl. controlled, unblinded, dose-ranging; crystalline atorvastatin	56 atorv 9 placebo	mean 58 yrs 22 men 43 women	LDL-C >160 and <250, TG <400	LDL 191 190 TG 185 176	6 weeks placebo run-in, 6 weeks pl, atorv 10, 20, 40, 60, 80 mg QD
981-25	16-week, pl. controlled, 2X blind, dose-ranging, safety and efficacy	172 atorv 56 placebo	mean 56 yrs 142 men 86 women	LDL-C >160 and <250, TG <400	LDL 218 200 TG 186 171	6-week pl. run-in, 16 weeks pl, atorv 10, 40, 80 mg QD
981-10	6-month, pl. controlled, 2X blind, 10 mg fixed dose	20 atorv 19 placebo	mean 54 yrs 22 men 17 women	LDL-C >160 and <250, TG <400	LDL 196 188 TG 162 169	6-week placebo run-in, 26 weeks pl., atorv 10 mg QD

The sponsor has identified studies 981-04 and 981-10 as the two pivotal proof of efficacy trials in this NDA. The Division agreed to this designation in meetings with the sponsor. Note that 981-96 is the important replication of 981-04 using crystalline atorvastatin, virtually identical to the trial using amorphous atorvastatin save for the following:(1) the addition of a 60-mg dose and elimination of the 2.5- and 5-mg doses, and (2) the use of nonblinded study medication. Study 981-25 was a longer term dose-ranging efficacy and safety study that serves not only to demonstrate the durability of the response to drug but also by its size, perhaps giving a more accurate point estimate of the true effect of atorvastatin in this population

Within the individual studies, despite the small sizes, the treatment groups were fairly well matched at baseline for age gender, and plasma lipids. While, as implied above, the small numbers studied does not allow for an accurate estimate of the true population effect of the drug; nevertheless, the known absence of a placebo effect in the therapy of dyslipidemias in conjunction with the observed alterations associated with active drug leave little question as to the efficacy of this agent.

Efficacy results

The relevant efficacy data at study termination are shown in the table below. The mean percent changes from baseline are adjusted means based on the ANCOVA model with effects due to treatment, center, and baseline as covariate.

Table 7.1.2. Efficacy results from placebo-controlled trials

		Atorvastatin (mg)							
		Placebo	2.5	5	10	20	40	60	80
Parameter	Study #								
	981-04	8 (2.7)	-25* (2.8)	-29* (2.6)	-41* (2.8)	-44* (2.9)	-50* (2.8)		-61* (2.8)
LDL-C	981-96	0 (3.6)			-37* (3.3)	-42* (3.4)	-50* (3.4)	-52* (3.0)	-59* (3.1)
% change (SE)	981-25	2 (1.8)			-32* (1.8)		-46* (1.8)		-53* (1.9)
	981-10	1 (2.3)			-33* (2.2)				
	981-04	-1 (6.3)	-10 (6.6)	-25* (6.1)	-14 (6.6)	-33* (6.9)	-25 (6.7)		-27 (6.6)
TG	981-96	26 (7.1)			-27* (6.6)	-23* (6.7)	-33* (6.9)	-37* (5.9)	-45* (6.1)
% change (SE)	981-25	4 (3.7)			-21* (3.6)		-22* (3.6)		-30* (3.7)
	981-10	15 (7.0)			-17* (6.6)				
	981-04	-2 (3.4)	5 (3.6)	8 (3.3)	4 (3.5)	12* (3.7)	-3 (3.6)		3 (3.5)
HDL-C	981-96	-3 (4.0)			8 (3.7)	8 (3.8)	13 (3.9)*	3 (3.4)	7 (3.6)
% change (SE)	981-25	3 (2.0)			9* (1.5)		10* (2.0)		8 (2.0)
	981-10	-3 (2.60			4 (2.5)				

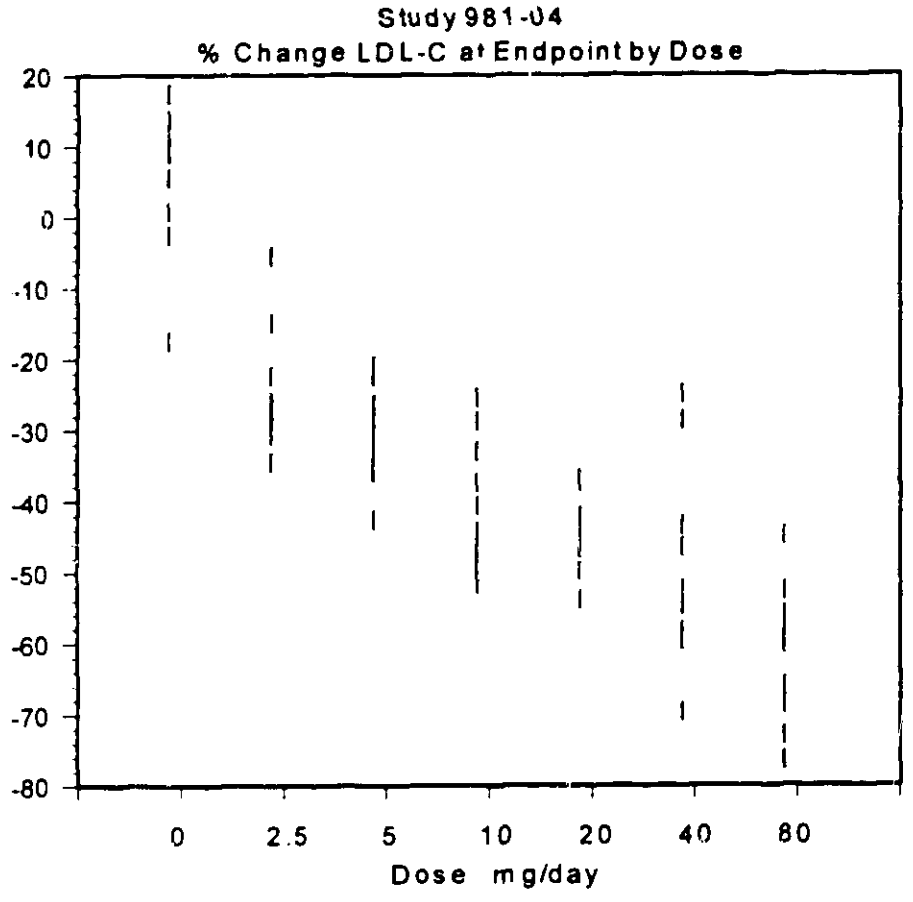
* significantly different from placebo, ANCOVA, $p<0.05$

LDL-C lowering:

The most marked effect of atorvastatin on plasma lipids is, as expected by its mechanism of action, a reduction in LDL-C. Not shown here is the parallel response in Apo B across the dose range studied. The mean percent changes in LDL-C levels were all statistically significantly different from placebo. Indeed it is again important to note that in patients with primary hyperlipidemias, there is no placebo effect with regard to LDL-C. The dose-dependence of the effect observed is consistent with the pharmacologic class, all members of which act by inhibiting hepatic cholesterol biosynthesis and increasing clearance of LDL by up-regulating the

The scatter plot below shows the individual end-of-study results for percent lowering of LDL-C from baseline in study 981-04. It is included to illustrate the clear dose-dependent trend as well as the variability in individual responses to drug.

Figure 7.1.1 Percent LDL-C lowering by dose. 981-04



Triglyceride lowering
The triglyceride lowering effect of atorvastatin in this patient population (see table, above), while real, is less consistent across individual patients (note the larger standard errors) and non-dose-dependent. Nevertheless, the mean percent changes from baseline in triglycerides were, in all but a few cases, statistically significantly different from placebo.

Effect on HDL, Apo AI, Lp(a):
By contrast, atorvastatin, like the other HMGRIs does not consistently raise HDL or Apo AI, the principal apoprotein of HDL. However, although not shown here, the ratio of non-HDL cholesterol to HDL cholesterol does improve (by falling) consistently in the atorvastatin groups. This is perhaps a marker of an overall more favorable lipid profile.

Another atherogenic lipoprotein, Lp(a), was also inconsistently reduced by atorvastatin, with the only observed significant response being a -14.2% mean change from baseline at the 80 mg dose in study 981-04.

Other efficacy issues pertaining to labeling

981-04: Dose-ranging study with amorphous atorvastatin
In study 981-04, the time to maximum mean LDL-C lowering effect was investigated with results showing that by two weeks of therapy, 90% of the mean effect had occurred. By 4 weeks of double-blind therapy, maximum mean lowering at a given dose had occurred. These results are generally consistent with the effects of the other statins. The sponsor recommends dose adjustment every two to four weeks, justified by these data.

981-96: Dose-ranging, crystalline atorvastatin

The results of study 981-96 show that the efficacy of the amorphous and crystalline forms of atorvastatin are therapeutically similar across the dose range of 10 to 80 mg/day. This study serves as an adequate bridging efficacy study for crystalline atorvastatin. These data in conjunction with the biopharmacology data indicating only a small increase in the rate but not in the extent of absorption of crystalline as compared to amorphous atorvastatin are sufficient evidence to support their clinical interchangeability. The relevant safety data will be addressed later in the review.

Conclusions

Although no direct comparisons to other agents were made in any of these trials, examination of the table shows that, clearly, atorvastatin appears more potent on a per mg basis as an LDL-C-lowering agent than any of the currently marketed statins. Indeed, the >50% LDL-C lowering achieved in the 3 studies using the 80 mg dose markedly exceeds the historical data for the highest marketed doses of the other agents. Comparative efficacy will be discussed in detail in the next section.

In summary, in these studies, all in similar populations, atorvastatin therapy was associated with significant, dose-related reductions from baseline of LDL-C. Atorvastatin also consistently lowered TG, though in a non-dose-dependent manner, and had inconsistent, small effects on HDL-C. Lp(a) was not significantly affected. The range of LDL-C lowering from baseline in response to therapy with from 10 to 80 mg of atorvastatin per day was -32 to -61%. In the largest of these studies, 981-25, the maximum mean lowering from baseline was 53% for the 57 patients randomized to atorvastatin 80 mg daily.

The pooled efficacy results from these four studies and study 981-08, a placebo-controlled trial comparing atorvastatin 10 mg to lovastatin 20 mg for the first 16 weeks are presented in the table below. The data presented are better estimates of the true treatment effect of atorvastatin in moderate hypercholesterolemics than those from the studies taken individually.

Table 7.1.3. Mean percent change from baseline. Studies 981-04, 981-08, 981-10, 981-25, 981-96 combined

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	347	-7%	-10%	-7%	-1%	+3%	-11%
10	1476	-27%	-37%	-29%	-17%	+7%	-38%
20	20	-33%	-43%	-36%	-28%	+10%	-42%
40	77	-34%	-47%	-39%	-23%	+9%	-46%
60	13	-40%	-51%	-41%	-35%	+3%	-50%
80	78	-42%	-55%	-46%	-33%	+7%	-53%

The laboratory and clinical adverse events observed in these studies will be addressed in the overall safety review of NDA 20-702.

Applicability to proposed labeling

The findings of these studies support claims in the proposed label with regard to the dose-related effect of atorvastatin in total-C, LDL-C, and Apo B lowering, as well as the efficacy compared to placebo in TG lowering in patients with Types IIa and IIb hyperlipoproteinemia. In addition, the time course of the effect monitored in studies 981-04 and -96 supports recommendations for a 2 to 4 week interval between dose titrations.

7.2 Studies comparing atorvastatin to other lipid lowering agents

Introduction

The studies discussed in this section were designed to compare the effects of atorvastatin to those of other HMGRIs and to bile acid binding resins in patients with moderate hypercholesterolemia (Type IIa and b). In addition, the data from these studies constitute the comparison of the safety and tolerability of atorvastatin to those of the three most widely used marketed HMGRIs, pravastatin, simvastatin, and lovastatin. The principal purpose in reviewing the efficacy results of these studies was to validate the claims made in the proposed package insert with regard to the superiority of atorvastatin over competitor single agents or combination therapy in both absolute percent lowering of LDL-C from baseline and in the percent of patients reaching LDL-C goals based on NCEP guidelines. The principal data cited in proposed labeling are from the fixed dose periods of the comparison studies, prior to dose titration. Safety comparisons will be addressed in a separate section.

Comparison of atorvastatin to other HMGRIs

The table below lists the principal comparative studies and outlines their relevant characteristics.

Table 7.2.1. Comparative studies or atorvastatin and other reductase inhibitors

Study #	General design	Enrollment	Age/gender	Lipid inclusion	LDL-C goal	Dose regimen
1-07	12 wk, open-label, 8-sequence, 2-period crossover: atorv vs prava and simva	46 ator/prav 46 ator/simv	59 yrs mean 45 men 47 women	LDL-C >160 and <240; TG <300	none	4 wk pl run-in; 4 week Ator 5 or 20 or simva 10 or prava 20; 4 wk washout; 4 week crossover to Ator 5 or 20 or simva 10 or prava 20
981-08	52 wk, pl controlled, 2X blind, atorv vs lova	70 pl/Ator 67 pl/Lova 719 Ator 193 Lova	57 yrs mean 610 men 439 women	LDL-C > 145 and <250 on diet, TG <400	NCEP*	6 wk pl run-in; 16 wk 2X blind pl, Ator 10, Lova 20; 6wk Ator 10, Lova 20; 30 wk after dose titration Ator 10 or 20 vs Lova 20 or 40
981-09	52 wk, 2X blind, ator vs prava dose titration	227 ator 78 prava	57 yrs mean 139 men 166 women	LDL-C >160 and <250 and TG <400	<130	6 wk pl run-in; 16 wk 2X blind ator 10 or prava 20; 36 wk 2X blind after dose titration ator 10 or 20 vs prava 20 or 40
981-37	52 wk, 2X blind, ator vs simva dose titration	132 ator 45 simva	57 yrs 94 men 83 women	LDL-C >145 and <300 on diet; TG <400	<130	6 wk pl run-in; 16 wk 2X blind ator 10 or simva 10; 36 wk 2X blind after dose titration ator 10 or 20 vs simva 10 or 20
981-57	52 wk, 2X blind, ator vs prava dose titration	224 ator 73 prava	59 yrs 165 men 132 women	LDL-C >160 and <250, TG <400	EAS**	6 wk pl run-in; 8 wk 2X blind ator 10 or 20 or prava 20 or 40; 8 wk 2X blind ator 10, 20, 40 or prava 20 or 40; 36 wk 2X blind ator 10, 20, 40, or 80 or prava 20 or 40

* National Cholesterol Education Program. Goal LDL-C determined by baseline LDL-C and presence of concomitant risk factors.

**European Atherosclerosis Society. Initial dose was based on risk status by EAS guidelines (baseline LDL-C

level and concomitant CHD risk factors). Those at mild to moderate risk were assigned goal of ≤130 mg/dl LDL-C and those at high risk ≤115 mg/dl.

Results

The head-to-head comparative studies of atorvastatin and marketed HMGRIs submitted to the NDA were well-designed and implemented, with comparable baseline characteristic between the groups and with few dropouts. The results of comparator studies 981-07, 08, 09, and 37 listed in the table below of percent changes from baseline by drug and dose prior to any titrations (week 15 measurements for all studies) again demonstrate the reproducibility of the effect of atorvastatin in lowering LDL-C and TG. The approximately 35% mean reduction from baseline in LDL-C seen across the 10 mg atorvastatin treatment groups in three distinct studies is consistent with the degree of reduction seen at this dose in other studies in the NDA.

Validity of comparative data:

The sponsor has proposed the inclusion of 16-week lipid data from the three double-blind studies, 981-08, -09, -37. The comparative data from these trials are validated in part by the reproducibility seen across the current studies (including 981-07) in lipid lowering, and the general consistency of these trial results with historical efficacy data documenting the LDL-C lowering effect of the marketed HMGRIs. Specifically, the response to pravastatin and simvastatin is similar across the studies presented here (see table 7.2.2). With regard to the LDL-C lowering effect of lovastatin, the results in study 981-08 are consistent with the published efficacy of lovastatin (EXCEL: -27% in the 20 mg group). The exceptions are that the published and labeled LDL-C lowering efficacy of pravastatin (WOSCOPS: -25% in the 40 mg group, label: -32% in the 20 mg group), and simvastatin (label: -33% in the 10 mg group) are at some variance with the results seen in the present NDA. Notwithstanding this, the comparisons are valid as all were successfully randomized and implemented, and all but 981-07 were blinded.

The system of blinding should be clarified, again to support the study designs as capable of producing valid comparative data. In studies 981-08, -09, -37, and -57, patients were supplied with two bottles of tablets, one containing the drug to which each was randomized and the other a placebo that matched the active comparator drug assigned to the other treatment group. Patients were to take one tablet from each bottle at bedtime. There was no reprocessing of atorvastatin or comparator drugs in order to effect blinding.

Table 7.2.2. Mean changes in LDL-C and TG from baseline in 4 comparative trials

		Treatment						
		Placebo	Ator 5mg	Ator 10mg	Ator 20 mg	Lova 20mg	Prava 20mg	Simva 10mg
Parameter	Study #							
	981-07		-27.3(39)		-44.2*(39)		-23.9(38)	-27.5(38)
LDL-C	981-08	1(133)		-36**(707)		-27(191)		
% change	981-09			-35**(222)			-23(77)	
(N)	981-37			-37**(132)				-30(45)
	981-07		-15.8(39)		-23.3*(39)		-11.4(38)	-7.5(38)
TG	981-08	4(133)		-17**(707)		-6(191)		
% change	981-09			-17**(222)			-9(77)	
(N)	981-37			-23**(132)				-15(45)

* superior to simva 10 and prava 20, $p<.05$
**significantly different than comparator HMGRIs, ANCOVA, $p\leq.05$

981-07: 8-sequence crossover design; results from combined cohorts treated for 4 weeks, regardless of period
981-08: parallel group design; placebo groups switched to one of two active treatments at 16 weeks and then titrated if not at LDL-C goal at week 22
981-09, -37: parallel group design, with titration as needed at week 16

For -08, -09, -37, efficacy results shown are at week 16. Despite subsequent dose titration (Ator 10-20, Lova 20-40, Prava 20-40, Simva 10-20) to meet LDL-C goals, mean % changes from baseline for LDL-C and TG in the three drug groups at 52 weeks were not substantially changed.

981-07: 8-sequence crossover study

For study 981-07, an open-label crossover study, the figures given are the mean percent changes from pre-treatment baseline for the combined cohorts treated for 4 weeks, regardless of period, with either of two doses of atorvastatin (5 and 20 mg) or pravastatin 20 mg or simvastatin 10 mg. These figures are for the evaluable patient data set. The baseline characteristics of the patients randomized to each of the eight treatment sequences were similar with regard to gender, age, and serum lipids. In this trial, LDL-C lowering with atorvastatin 20 mg was statistically significantly greater than that with the starting doses of both pravastatin (20 mg) and simvastatin (10 mg). Atorvastatin 20 mg was also more effective in lowering total cholesterol, Apo B, and triglycerides. None of the agents had any consistent impact on HDL-C or Lp(a).

981-08, 09, 37: 1-year, blinded comparative studies

The 16-week results of the three 52-week studies, 981-08, 09, and 37, are cited in the proposed package insert for atorvastatin. In all three of these trials, doses of HMGRI were adjusted after week 16 in order to achieve LDL-C goals, either based on risk category per NCEP guidelines (981-08) or arbitrarily set at 130 mg/dl (981-09, 37). In these three comparative trials, after 16 weeks, lowering of LDL-C and TG in response to the starting dose of atorvastatin (10 mg) was statistically significantly greater than that in response to starting doses of lovastatin, pravastatin,

and simvastatin, respectively. Within each study, the treatment groups were well matched at baseline for characteristics as age, gender, LDL-C, Fredrickson phenotypes, and incidence of heterozygous FH.

Comparative efficacy in reducing LDL-C to goal levels:
The table below summarizes the comparative efficacy of atorvastatin and the other studied HMGRIs in reducing LDL-C to goal at the end of 16 weeks and at the end of the 52-week trial period. The greater potency of atorvastatin in lowering LDL-C from baseline, as might be predicted, results in a higher percentage of atorvastatin-treated patients reaching pre-defined LDL-C goals. The range of outcomes in the atorvastatin groups across the three studies, on both the uniform starting dose of 10 mg (16 week data) and after dose titration as needed (52-week data) does not affect the finding that atorvastatin exceeded the comparator drugs in this measure of efficacy.

Table 7.2.3. Percent of patients reaching LDL-C goals in comparative studies

			Treatment				
			Placebo	Ator 10/20	Lova 20/40	Prava 20/40	Simva 10/20
Parameter	Week of study	Study #					
% reaching LDL-C goals	16	981-08	7%	74%	55%		
		981-09		65%		19%	
		981-37		46%			27%
	52	981-08	*	78%	53%		
		981-09		71%		26%	
		981-37		50%			48%

*Placebo crossed to active treatment at week 16.

981-08: LDL-C goals set by NCEP guidelines
981-09,-37: LDL-C goals <130 mg/dl for all patients

The explanation for the inconsistency of the atorvastatin response for this parameter may lie the differences in mean baseline LDL-C for the individual study populations (table 7.2.4). The mean baseline LDL-C of 212 mg/dl in the 981-37 population was considerably higher than in the other two studies, and this is the study with the lowest responder rate with regard to percent of patients reaching LDL-C goal. In addition to the lower mean baseline LDL-C, the fact that the treatment goals in study 981-08 were based on risk factor stratification according to NCEP guidelines (and therefore perhaps less stringent than the goals arbitrarily set at 130 mg/dl in the other two studies) may have contributed to the high responder rate in this study. The role of the increased percentages of FH heterozygotes in 981-09 and 981-37 is not clear.

Table 7.2.4. Baseline characteristics of study populations in comparative studies

	Mean LDL-C	Race (% non-white)	Gender (male:female)	% FH*	Mean age
Study #					
981-08	190	8	60:40	13	58
981-09	195	0	46:54	25	57
981-37	212	2	53:47	26	57

*heterozygous familial hypercholesterolemia by family history, clinical characteristics

981-57: European study

One other study comparing the effects of atorvastatin to those of pravastatin (981-57) is presented in the NDA. This was a trial conducted in Europe in which men and women with moderate hypercholesterolemia were randomized to receive either atorvastatin or pravastatin (3:1) and given a starting dose based on baseline LDL-C and risk factors according to EAS guidelines, with the goal LDL-C also based on CHD risk. There were two initial 8-week treatment periods, at the end of each of which dose was titrated if inadequate response had been achieved up to that point. Dose was maintained for the final 36 weeks of the study. The table below shows the distribution of patients according to drug, dose, and duration of treatment.

Table 7.2.5. Drug exposure by dose in Study 981-57

	Ator 10	Ator 20	Ator 40	Ator 80	All Ator	Prava 20	Prava 40	All Prava
N	98	173	93	37	222	28	70	72
Mean days exposed	225	169	176	236	344	96	322	349
Total exposure	22,094	29,310	16,376	8,718	76,318	2,677	22,571	25,134

Although two-thirds of the atorvastatin exposure was at the 10 and 20 mg doses while nearly 90% of the pravastatin exposure was at the maximum labeled dose of 40 mg, at 52 weeks, 51% of atorvastatin patients as compared to only 20% of pravastatin patients had reached goal LDL-C levels. These data are echoed in a greater mean percent reduction in LDL-C from baseline in the atorvastatin group (-39% vs -29%) and simply corroborate the greater potency in LDL-C lowering of atorvastatin.

Comments on labeling:

With regard to the claims in labeling pertaining to these comparative data, it must be remembered that the starting dose of atorvastatin was likely chosen precisely because of the relatively high degree of LDL-C lowering it induces. The minimum effective dose of atorvastatin producing a clinically significant decrease in LDL-C is closer to 2.5 to 5 mg daily. While 10 mg of atorvastatin is clearly more potent than the recommended starting doses of pravastatin, lovastatin, and simvastatin, there are doses of these other drugs that are equally or more potent. By the same token, depending on baseline LDL-C, on the degree of LDL-C lowering required to meet NCEP goals, for many patients, other agents will be effective in reducing LDL-C to goal levels.

The studies reviewed here were well-designed and implemented, with comparable groups at baseline within studies and with very few dropouts. As such, the comparative data are valid and do support claims of superiority for the 10 mg dose over the specific doses of comparator studied. In addition to greater potency on a per mg basis, in an absolute sense, the proposed dosage range for atorvastatin allows for significantly greater percent LDL-C reductions from baseline than can be achieved across the potency and dose ranges of the other marketed agents in patients with moderate hypercholesterolemia.

As to the presentation of these data in the label for atorvastatin, the inclusion of 95% confidence limits for the differences in LDL-C lowering between atorvastatin and comparator agent seems appropriate. As was presented earlier, there is significant variability in the response to atorvastatin and to the other statins in LDL-C lowering. Although, the superiority of atorvastatin in LDL-C lowering in the comparative trials was statistically significant in all cases, nevertheless, the lower limits of the confidence intervals for the differences in response approach values that are not clinically significant in a number of cases. The communication of this type of information to physicians and to patients is important in allowing consumers to make informed decisions regarding choice of therapy. Finally, the label should include clarification in the text to the effect that the clinical trial data in no way imply that the reductions in LDL-C observed with atorvastatin 10 mg might not be equaled or exceeded with higher doses of the comparator drugs. Specific language will be suggested in the labeling review.

No data are provided which support claims in labeling referring to the comparison trials of efficacy in reducing LDL-C to NCEP goals. That is, because 2 of 3 of the 1-year studies did not use NCEP goals (but rather arbitrarily set goal at <130 mg/dl LDL-C for all patients), it is not apparent what percentage of the patients in those studies met NCEP goals.

Comparative efficacy of atorvastatin and colestipol and the combination of the two

Study 981-43
Objectives/design
One final study that speaks to the efficacy of atorvastatin in patients with moderate Type IIa and IIb hypercholesterolemia was study 981-43, an open label, multicenter, randomized, parallel arm, 12-week study comparing the LDL-C lowering effect of atorvastatin 10 mg with those of colestipol 10 g/day and of the combination of atorvastatin plus colestipol. Lipid entry criteria were LDL-C >160 and TG <350. A total of 106 men and women (~50:50) were randomized (2:2:1) and underwent an 8 week diet baseline period. Those patients randomized to colestipol or to the combination started on a colestipol dose of 5 gm/day, which was increased to 10 g/day after 2 weeks. Active treatment was continued for a total of 12 weeks. The primary endpoint of the trial was mean percent change from baseline in LDL-C.

Study implementation:
The intent-to-treat sample contained 105 patients as one patient had no post-randomization lipid determinations. The three treatment groups were well matched at baseline for average age, gender make-up, race, and serum lipids.

Compliance with protocol requirements was, as expected, greatest for the atorvastatin monotherapy group (95% completed study, 90% compliant with regimen), and less so for the combination therapy groups (90% completed, 75% compliant) and least for the colestipol monotherapy group (80% completed, 70% compliant). Colestipol dose could be adjusted downward by the study coordinator based on patient intolerance, but any interval during which the dose was less than that called for in the protocol was considered a period of non-compliance. Suffice it to say that the frequent follow-up if anything optimized therapy with the less tolerable resin.

Results:
The pertinent efficacy results are shown in the table.

Table 7.2.6. Study 981-43 efficacy results

	Ator 10 mg N=41	Colest 5-10g N=44	Combination N=20
Mean % change in:			
LDL-C	-35*	-22	-45**
HDL-C	12	5	13
TG	-17*	18	-4
VLDL-C	-35*	9	-28

* significantly different from colestipol monotherapy, p<.001, ANOVA (effects of treatment and center)
** significantly different from atorvastatin monotherapy, p<.01, ANOVA

For the ITT sample, at the end of 12 weeks, atorvastatin was superior to colestipol in lowering

LDL-C, though, as is the case with the other statins in combination with resins, atorvastatin plus colestipol had an additive effect that exceeded that of either monotherapy. This relationship held true for the lowering of total-C, Apo B. No significant differences were observe between treatment groups in change in HDL-C or Apo AI.

For VLDL-C and TG lowering effect, atorvastatin monotherapy was statistically significantly superior to colestipol monotherapy or to the combination of the two in mean percent change from baseline. This is in keeping with the mechanism of action of the resins, which stimulate bile acid synthesis in part via an induction of the HMG-CoA reductase enzyme. While this is accompanied by an increase in the expression of LDL receptors with consequent increase clearance of LDL-C, there has been frequently observed an increase in VLDL-C and TG (VLDL-TG) likely as a result of the increase in HMG-CoA reductase activity.

In sum, as for the other HMGRIs, there is a synergistic effect of atorvastatin and colestipol in LDL-C lowering, though the trade-off is an increase in VLDL and TG due to the resin. The safety and tolerability data from this study will be included in the overall safety summary.

Labeling
No specific references to this study exist in the proposed labeling.

7.3 The effect of atorvastatin in patients with hypertriglyceridemia:

A non-dose-dependent lowering of TG was observed in the studies in patients with primary hypercholesterolemia (primarily Type IIa). When the trials were considered in the aggregate, results showed that atorvastatin induced mean percent reductions in TG and VLDL-C that were significantly different from placebo at doses from 5 to 80 mg.

The trials summarized in this section were undertaken to assess the effect of atorvastatin as a cholesterol and triglyceride lowering agent in patients with combined hyperlipidemia (Type IIb, elevation in LDL and VLDL) and isolated hypertriglyceridemia (Type IV, elevation in VLDL or IDL) in the absence of metabolic disorders possibly influencing lipid or lipoprotein levels. Patients taking insulin or oral hypoglycemic agents were specifically excluded. The table below summarizes the characteristics of the three trials. The results of 981-38 are most relevant to labeling, as this was the only one of the three studies that was placebo controlled. Because of the absence of placebo effects in disorders of lipid metabolism, however, the results of the other two studies need not be overlooked. Indeed, they corroborate the results of 981-38.

Table 7.3.1. Trials in patients with hypertriglyceridemia

Study #	General design	enrollment	Age/gender	Lipid inclusion	Fredrickson phenotype*	Dose regimen
981-38	4-week, 2X blind, pl controlled, dose-ranging	42 Ator 14 placebo	mean 51 yrs 48 men 8 women	TG ≥350**	II b 18 IV 38	4-wk placebo run-in; 4-wk 2X blind pl, Ator 5, 20, 80
981-42	12-wk open-label Ator vs niacin	55 Ator 53 Niacin	mean 55 yrs 70 men 38 women	TC ≥200, TG ≥200 and ≤800, apoB≥110	II b 83 IV 25	6-wk placebo run-in; 12-wk open label Ator 10, Niacin 1 g TID
981-55	24-wk open-label Ator vs fenofibrate	47 Ator 52 feno	mean 52 yrs 68 men 31 women	TC ≥200, TG ≥200 and ≤800, apoB ≥110	II a/b 79 IV 20	12-wk open label Ator 10, Feno100 TID; 12 wk open-label Ator 20, Feno 100 TID

* Type II a: Primary hypercholesterolemia (LDL-C≥135, TG<200)
Type II b: combined hyperlipidemia (LDL-C ≥135, TG≥200)
Type IV: isolated hypertriglyceridemia (LDL-C<135, TG≥200)

In study 981-55, there were a total of 6 patients with Type II a hyperlipoproteinemia. The other studies had only hypertriglyceridemic patients with or without hypercholesterolemia (Types II b and IV)

** Randomization in this trial was stratified by baseline LDL-C ≤160 and >160.

Enrollment:
The first study, 981-38, a small placebo-controlled dose-ranging study, enrolled mostly Type IV patients (67%) while the other two trials, 981-42 and -55, enrolled mostly Type IIb patients (~80%). Within each study, treatment groups were fairly well-matched at baseline for variables including age, gender make-up, serum lipids, Fredrickson phenotype, and body mass index. In study 981-38, the randomization was stratified by baseline LDL-C <160 and ≥160 mg/dl.

Results
The table summarizes the principal efficacy results of the three studies by dose of drug and by Fredrickson phenotype. The placebo group results are not shown for study 981-38. Overall, atorvastatin appears effective at lowering LDL-C, TG, VLDL, and the ratio of non-HDL-C to

HDL-C in patients with hypertriglyceridemia. In head to head comparator studies, niacin and fenofibrate appear superior to atorvastatin in lowering TG and VLDL-C. Importantly, however, because of its dramatic LDL-C lowering effect, atorvastatin effects greater (and therefore more favorable) reductions in the ratio of non-HDL-C to HDL-C.

Table 7.3.2. Effect of atorvastatin in the treatment of patients with hypertriglyceridemia

		Type II b					Type IV				
		Ator 10	Ator 20	Ator 80	Niacin	Feno	Ator 10	Ator 20	Ator 80	Niacin	Feno
% change	Study #										
	981-38		-43*	-51*				-29*	-35*		
LDL-C	981-42	-33**			-8		-15**			+14	
	981-55		-39**			-7		-28**			+27
	981-38		-32	-31				-32*	-50*		
TG	981-42	-16			-29**		-36			-29	
	981-55		-27			-39		-34			-57**
	981-38		-46	-47				-44*	-64*		
VLDL-C	981-42	-28			-39		-43			-36	
	981-55		-39			-50		-36			-73**
	981-38		-56	49				-43*	-57*		
nonH/H	981-42	-34			-32		-34			-19	
	981-55		-44**			-32		-36			-35

nonH/H: non HDL-C/HDL-C ratio. A low ratio may be a marker for decreased CHD risk.
For study 981-55, data shown are for week 24, after 12 weeks of therapy with Ator 20 and 24 weeks of therapy with Feno 300.
* Significantly different from placebo (results not shown).
** Significantly different from comparator drug

Study 981-38

In this study, atorvastatin effectively lowered LDL-C, relative to placebo, regardless of Fredrickson phenotype, though the degree of lowering was less dramatic in patients with isolated hypertriglyceridemia. With regard to TG and VLDL-C lowering, both the 20 and 80 mg doses were associated with statistically significant reductions relative to placebo in the Type IV patients. The trends in TG and VLDL-C lowering were dose-related in both Type IIb and Type IV groups, though for the 18 Type IIb patients, at no dose were the results significantly different from placebo, likely due to the small N studied.

When all patients were taken together, irrespective of Fredrickson type, results (not shown) revealed that atorvastatin reduced total TG in a dose-related manner up to 43% at the 80 mg dose after 4 weeks of treatment.

Analysis by LDL-C strata showed that the one patient with baseline LDL-C >160 mg/dl and baseline TG ~400 mg/dl had a 76% reduction in TG on atorvastatin 80 mg. The mean percent reduction in TG in the 11 patients with LDL-C ≤160 mg/dl treated with atorvastatin 80 mg was 40%. At all other doses, TG responses were similar between LDL-C strata.

Finally, when cholesterol and TG changes were assessed in the various lipoprotein fractions, atorvastatin was found to reduce both in virtually all fractions (LDL-C, LDL-TG, VLDL-C, VLDL-TG, HDL-TG). The exception was a significant increase in HDL-C at the 80 mg dose. In other words, VLDL-TG was reduced without a redistribution of TG into other lipoprotein fractions and paralleled the reduction in LDL-C expected from an agent of the HMGRI class. The triglyceride-lowering effect of atorvastatin is unique among HMGRIs.

Studies 981-42, -55

In these comparative trials, atorvastatin was significantly more effective than either niacin 3 g/day or fenofibrate 300 mg/day in lowering LDL-C. Indeed, note the elevation in LDL-C seen in response to niacin and fenofibrate in the patients with Type IV HELP, the so-called beta-shift seen with increased catabolism of VLDL in patients with hypertriglyceridemia. The beta-shift did not occur with atorvastatin.

These data suggest a dual mechanism of action for atorvastatin in lowering TG. On the one hand, the increased expression of LDL (B, E) receptors in response to HMGRI therapy increases the clearance of VLDL remnants, thus potentially lowering VLDL-TG. In addition, the inhibition of cholesterol biosynthesis limits cholesterol as a component of nascent VLDL particles, and may decrease the synthesis and secretion of triglyceride-containing VLDL and thus levels of total TG.

In both Type IIb and Type IV patients, niacin and fenofibrate were more effective at lowering TG and VLDL-C than was atorvastatin, though the differences were significant only for niacin in the Type IIb groups and for fenofibrate in the Type IV patient cohort. When each study was analyzed separately (data not shown), without distinguishing effects by phenotype, both niacin and fenofibrate lowered TG in all but the LDL fraction to a greater extent than did atorvastatin. In addition, each was better than atorvastatin in its impact on HDL-C inducing 21 to 24% increases while atorvastatin had minimal effects.

On balance, when compared to atorvastatin, because the increase in LDL-C seen with niacin and fenofibrate in these studies was coupled with a greater reduction in VLDL-C and significant increases in HDL-C, the net impact of the therapies are reflected in the generally comparable changes across treatments and Fredrickson phenotypes in the ratio of non-HDL-C to HDL-C.

In sum, while no claims of superiority over traditional agents used in the treatment of hypertriglyceridemia can be made for atorvastatin based on these trials, the net effect of atorvastatin is significantly different than placebo. While the clinical impact of such therapy is not known, these data suggest atorvastatin as an effective, potentially useful drug in the treatment of combined hyperlipidemia and isolated hypertriglyceridemia.

Labeling

The sponsor makes no comparative claims in the proposed label with regard to TG lowering. The findings of these studies support the efficacy of atorvastatin in patients with hypertriglyceridemia, either isolated or in the setting of mixed dyslipidemia.

7.4 Studies in patients with severe hypercholesterolemia, predominantly heterozygous FH:

The two trials briefly reviewed in this section addressed the efficacy of atorvastatin 80 mg in the treatment of patients with markedly elevated LDL-C and TC (LDL-C >250), most of whom had heterozygous FH defined either by the presence of tendinous xanthomas and a family history with evidence of an autosomal mode of inheritance, or by the presence of a genetically defined LDL-receptor gene defect.

Heterozygous FH patients are notoriously difficult to treat to NCEP goal, and usually require combination therapy even to approach target LDL-C levels. Indeed, although the NCEP has not specifically addressed these patients, based on a uniform high risk for premature coronary disease that exceeds the risk in the general hypercholesterolemic population, these patients probably should all be treated as though they have CHD, with goal LDL-C <100 mg/dl. The percentage of those reaching goal by risk factor strata in these studies will be reviewed for completeness. These trials serve as a logical lead-in to the discussion of the results of treatment in FH homozygotes. The overall efficacy in FH heterozygotes treated in this NDA is discussed later in a review of analyses performed on pooled data sets.

981-44: Pilot study
Design:
In the pilot study, 981-44, 22 patients (5 male, 17 female) with documented heterozygous FH were randomized (1:1) to receive either atorvastatin 40 mg BID or atorvastatin 80 mg QD for 6 weeks. These patients were selected from the clinic population of >500 FH heterozygotes at the University of Cape Town, South Africa. Lipid inclusion criteria were LDL-C>250 on strict diet and TG<400. Lipids were measured at baseline (4-week placebo and diet run-in), and after 2, 4, and 6 weeks of treatment. The 4 and 6-week lipid measurements were not significantly different.

Results:
Results showed no difference in lipid responses between the 2 treatment groups (Ator 40 BID, Ator 80/day), which were well matched at baseline for baseline LDL-C as well as for age, gender, and specific FH genetic defect. The results were therefore pooled and the data below are based on analysis of lipid determinations from all 22 study participants.

Table 7.4.1. Study 981-44: Efficacy results

	Week 2	Week 6
Lipids, % change in (SE):		
LDL-C	-43 (2)	-56 (2)
Total C	-35 (2)	-45 (2)
TG	-27 (4)	-31 (3)
HDL-C	+14 (5)	+23 (5)

This pilot study therefore demonstrates the efficacy of atorvastatin in the treatment of FH heterozygotes. The percentage reductions in plasma lipids were of similar magnitude to those observed in the other trials in this NDA in patients with other non-FH forms of hyperlipoproteinemia. In addition, though the sponsor makes no claims to this effect, the 56% LDL-C lowering in this small study exceeds the published efficacy of simvastatin, the most effective of the marketed HMGRIs, in heterozygous FH.

The study report suggests the possibility of a dual mechanism of action of atorvastatin in lowering cholesterol, due in part to its prolonged duration of activity in the liver. This mechanism of action involves inhibition of hepatic cholesterol synthesis leading to up regulation of LDL receptors with enhanced uptake of LDL-C from the circulation as well as a significant reduction in hepatic Apo B-containing lipoprotein synthesis and secretion.

981-56: 1-year study of Atorvastatin 80 mg in severe hypercholesterolemia

Design

Study 981-56 was a 52-week, randomized, parallel arm, active controlled study in 469 patients, nearly 70% of whom had heterozygous FH. The trial compared the lipid lowering efficacy of combination HMGRI plus bile acid binding resin with that of atorvastatin 80 mg monotherapy. A commonly used combination of simvastatin 40 mg plus colestipol 20 g/day served as one comparator treatment. In addition atorvastatin 40 plus colestipol 20 was employed in another group. The lipid inclusion criteria were LDL-C mean of two determinations >200 and <400 mg/dl and TG <400 mg/dl.

Treatments

After a 6 week diet lead-in phase, patients were randomized to three parallel treatment arms. For the first 4 weeks one group received atorvastatin 40 mg QD and the other two colestipol 5 gm BID. After 4 weeks and thereafter until study termination, the first group received atorvastatin 80 mg QD. The colestipol doses for the other two groups were increased to 10 gm BID for 12 weeks. Thereafter, one group was treated with simvastatin 20 mg QD followed by simvastatin 40 mg QD until study termination, and the other group received atorvastatin 20 followed by atorvastatin 40 mg QD until study termination. The 52 week efficacy data, then, reflect the response to treatment with either atorvastatin 80 mg QD, simvastatin 40 mg QD plus colestipol 10 g BID, or atorvastatin 40 mg QD plus colestipol 10 g BID. The longest exposure to atorvastatin 80 mg in this study was 48 weeks, and for atorvastatin 40 mg, the longest exposure

was 32 weeks. The total exposure to atorvastatin 80 mg was 69090 patient-days and the exposure to atorvastatin 40 gm plus colestipol 20 g was 45885 patient-days.

Disposition

The treatment groups were well-matched at baseline for gender, mean age and age distribution, race, body mass index, and phenotype, with a majority (66-68%) of patients having heterozygous FH. They were well matched for coronary risk factors as well and therefore for distribution among NCEP goal strata, as shown in the table below.

Table . Goal stratification at baseline in study 981-56

	Ator 80 N=189	Ator 40, Colest 20 N=124	Simva 40, Colest 20 N=124
% with goal LDL-C			
<100 mg/dl	24%	23%	17%
< 130 mg/dl	29%	31%	36%
< 160 mg/dl	47%	46%	47%

90% of the patients completed the 1 year study. The mean baseline LDL-C in all three groups was approximately 285 mg/dl. Thirty-two patients were excluded from the analysis because they had no lab analyses done after randomization.

The table summarizes the relevant efficacy outcomes at 52 weeks and includes the percentage of each group that reached NCEP goal stratified by the three target levels based on risk factor analysis.

Table . Efficacy data at 52 weeks. Study 981-56

	Ator 80 mg N=189	Ator 40 mg, Colestipol 20g N=124	Simva 40 mg, Colestipol 20g N=124
% change lipids			
LDL-C	-53*	-53*	-46
TG	-33**	-17	-10
HDL-C	7	9	10
% reaching NCEP goal (N)			
LDL-C <100	9 (4)	24 (7)	5 (1)
LDL-C <130	51 (28)	50 (19)	38 (17)
LDL-C <160	75 (67)	75 (43)	72 (41)

* different from simvastatin plus colestipol, ANCOVA, $p<.05$
** different from atorvastatin plus colestipol, ANCOVA, $p<.05$

Discussion/Labeling

Atorvastatin 80 mg/day was effective in lowering LDL-C and TG in these two studies, the pilot study exclusively in FH heterozygotes and 981-56 in which FH heterozygotes predominated (~70%). These findings justify a general claim as to the utility of this therapy in these patients in the label. The effects on LDL-C and TG were paralleled by favorable effects on total cholesterol, Apo B and VLDL-C. Atorvastatin 40 mg in combination with colestipol 20 g/day was as effective as atorvastatin 80 in reducing LDL-C, indeed more so in this trial in reducing LDL-C to NCEP goal in the high risk patient subset. The TG-lowering effects of atorvastatin 80 were, however, greater than those of either combination therapy. In general the therapy was well tolerated. Adverse events, associated adverse events, and clinical lab abnormalities will be discussed in the safety review of the NDA.

7.5 Atorvastatin in the treatment of FH homozygotes

Homozygous FH occurs extremely rarely, with an incidence of about 1 per million population worldwide. Patients may have serum total cholesterol as high as 1000 to 1200 mg/dl. The disease is characterized by cutaneous xanthomas and extensive premature atherosclerosis, often in the first and second decades of life. These patients have mutations in both LDL receptor genes that lead to very low or absent binding and uptake of circulating LDL-C. The treatment of choice is removal of LDL from plasma by one of several methods: total plasma exchange, immunoadsorption, membrane filtration, dextran sulfate absorption, and extracorporeal precipitation. These procedures are typically performed every two weeks. Other therapies include portacaval shunting, ileal bypass, and liver transplantation. Lipid lowering agents, including HMGRIs, are largely ineffective. Because of its long duration of action in the liver and because of its ability to reduce biosynthesis and secretion of lipoproteins by the liver, and in light of its superior effects in heterozygous FH, atorvastatin was studied in FH homozygotes. The two studies submitted to the NDA are reviewed here.

981-54: Pilot study

The first study, 981-54, was an 8-week pilot study of 8 patients from the clinic at the University of Cape Town, South Africa. Most had well-characterized LDL-receptor mutations with a range of LDLR binding from zero (receptor negative) to >15% of controls (receptor defective). Five were on regular plasmapheresis. The table below describes the study group.

Table 7.5.1. Study 981-54: Patient characteristics

Name	Age, gender	Plasmapheresis history	LDL-receptor binding
	24, F	17 yrs	High (>15% control)
	19, F	9 yrs	Low (5-15% control)
	19, M	9 yrs	Low
	32, M	19 yrs	Low
	13, M	6 yrs	Negative
	24, M	No	High
	25, M	No	Low
	23, F	2 yrs in past, now No	Negative

Design

After an 8 week placebo-diet run-in, patients were started on atorvastatin 80 mg/day and followed for 8 weeks. Clinic visits were every 2 weeks from the start of the placebo period. At each visit safety monitoring and measurement of plasma lipids was performed. Plasma mevalonate was also measured as a marker of inhibition of cholesterol biosynthesis. The five patients on plasmapheresis continued on this therapy biweekly. Each had a study to assess rebound of cholesterol during three separate intervals during the placebo and active treatment

periods. Baseline was defined as the average of the last 2 results prior to the active phase. Mean baseline LDL-C was 449 mg/dl for the five patients on plasmapheresis and 573 mg/dl for the three patients not on plasmapheresis. For patients on apheresis, lipid levels drawn just prior to plasmapheresis were used to assess efficacy of treatment.

The primary efficacy parameter was the percent of patients achieving >10% reduction in LDL-C from baseline. Secondary efficacy parameters included the percent change from baseline in plasma lipids, including LDL-C, TG, and HDL-C as well as changes in mevalonic acid.

Results

All patients had a decrease of at least 10% from baseline in LDL-C. The table below, from the investigator's report, shows the percent change in LDL-C in this study, but also includes the percent change previously achieved with simvastatin (no dose reported). The results are quite variable, but nevertheless impressive, clinically significant, and a marked improvement over simvastatin, which appeared to have an effect largely dependent on LDLR status, except for patient who showed a 30% LDL-C lowering on simvastatin though demonstrating low LDLR binding.

The results for TG and HDL-C were quite variable, as seen in table 7.5.2, though 6 of 8 patients showed a lowering of HDL-C. Lp(a) appeared to increase substantially in most patients. However, when these same patients were tested during study 981-80, the increases observed were inconsistent and less dramatic. The second table below (table 7.5.3) summarizes those results. The median Lp(a) level on treatment was statistically significantly increased from placebo. Preliminary data on Lp(a) turnover suggests that both the production and clearance rates of Lp(a) were increased with atorvastatin, the former more than the latter. Though epidemiologic data suggest that Lp(a) elevated above 20 to 30 mg/dl is an independent CHD risk factor, the significance of increases in Lp(a) as a risk factor is not known.

Table 7.5.2. Study 981-54: Week 8 efficacy results

			% change in lipids (Rx)		
Patient	LDL-C (Ator)	LDL-C (Simva)	TG (Ator)	HDL-C (Ator)	Lp(a) (Ator)

ND: not done

Table 7.5.3. Lp(a) in FH homozygotes. Study 981-80

Patient	Placebo	Atorvastatin
	14	17
	11	17
	28	57
	5	7
	66	72
	57	77
	32	33
	68	96
	20	47
	93	94
Median	30	52

Plasma mevalonate

Early morning plasma mevalonate was assayed as an indicator of cholesterol synthesis in the patients on plasmapheresis. Samples were collected during placebo and drug treatment periods, both pre-plasmapheresis and for three days following plasmapheresis. In the table below, note the relatively high levels on placebo and the apparent rebound within a few days after plasmapheresis. Also note that atorvastatin suppressed levels pre-plasmapheresis and appeared to prevent the rebound burst of synthesis after plasmapheresis.

Table 7.5.4. Study 981-54: Plasma mevalonate post-apheresis

Patient	Pre-PE Placebo	day 1 Placebo	day 2 Placebo	day 3 Placebo	Pre-PE Ator	day 1 Ator	day 2 Ator	day 3 Ator

PE: plasma exchange

This finding suggests a synergistic effect of atorvastatin and LDL apheresis on plasma LDL in FH homozygotes. The reduction in LDL uptake due to lowered plasma levels after apheresis and consequently reduced intrahepatic pools of cholesterol ester in addition to the inhibition of de novo synthesis of cholesterol by drug both contribute to inhibition of lipoprotein production and delay in the rebound of plasma LDL after apheresis (not shown). Indeed, this delay was clearly demonstrated in the five patients this study, all of whom maintained lower LDL-C levels throughout the interval between plasma exchanges on atorvastatin as compared to placebo.

Discussion
This pilot study serves to demonstrate the efficacy of atorvastatin in lowering LDL-C as an adjunct to plasmapheresis in patients with homozygous FH. In addition, atorvastatin was also effective in the three patients not on plasmapheresis. Atorvastatin delayed substantially the rebound in plasma LDL-C after apheresis and as such reduced the AUC for LDL-C in these patients.

Study 981-80: open label compassionate use study in FH homozygotes
This is an ongoing study under a treatment IND. Data from this study submitted to the NDA are restricted to results from those patients having completed 8 weeks of atorvastatin therapy at the time the NDA was prepared.

The objective of the study was to provide atorvastatin to patients with homozygous FH or to patients with severe hypercholesterolemia refractory to conventional therapy. Patients showing adequate response after 8 weeks of treatment would be enrolled in long-term open-label follow-up with regular safety monitoring.

Design:
Inclusion criteria included: 1)documented homozygous FH 2)LDL-C >220 mg/dl on maximally tolerated lipid lowering therapy and a <15% response to that therapy. Patients from age 6 onward were included.

Starting dose was 40 mg QD, save for a few patients, either children or seriously debilitated, who started as low as 10 mg/day. Dose was titrated after 4 weeks, with most patients thus treated with 80 mg/day up to the 8 week clinic visit. Visits were at study entry, 4, and 8 weeks. Safety laboratory, lipid sampling, and medication dispensing occurred at all three visits. Lipid data reported in the NDA are results at week 8 unless the highest titrated dose was reached after 8 weeks and those data were available at the time of preparation of the report. The results of the FH patients and those of the children are reported separately and are the focus of this review.

As for the other studies in this NDA, ALT or AST elevations >3X ULN on two consecutive measurements one week apart and CK>10X ULN on two consecutive measurements one week apart accompanied by muscle pain, tenderness, or weakness were considered clinically important laboratory abnormalities and recorded as adverse events.

Disposition:
Lipid data from 41 patients are included in the report. There were 29 patients with homozygous FH, including 5 receptor-negative individuals. 8 patients continued on plasmapheresis. 7 patients had previously been studied in 981-54. There were 9 patients 14 years old or younger. 35 patients were taking 80 mg atorvastatin at the time of lipid measurements. Two patients were

receiving 60 mg/day, one patients 30 mg/day, and 2 patients 20 mg/day.

Results: homozygous FH

24 patients with homozygous FH were treated with 80 mg/day atorvastatin for at least 4 weeks. 5 of 24 had not responded to therapy at the time of preparation of the study report. The table below summarizes the efficacy data for this group. The right-most column contains the results after exclusion of the 5 non-responders.

Table 7.5.5. Study 981-80: Results in FH homozygotes

	N=24	N=19 (non-resp excl)
% change LDL-C (range)	-18	-26
% change total-C (range)	-18	-24

There were 9 patients 14 years old or younger with homozygous FH, 4 of whom were treated with 80 mg atorvastatin. The mean reduction in LDL-C in this group was 21% with a range from

There were 11 patients with severe, unresponsive hypercholesterolemia with either heterozygous or compound heterozygous FH. The table below summarizes the data from these patients. The right-most column contains the results after the single non-responder was excluded.

Table 7.5.6. Study 981-80: Results in non-FH homozygotes

	N=9	N=8 (non-resp excl)
% change LDL-C (range)	-37	41
% change total-C (range)	-32	34

The listing of results for all the patients included in the study is reproduced from the study report and appears at the end of this section.

Safety:

Three patients withdrew due to adverse events. One patient (12-. developed a rash after

three days of treatment with atorvastatin 40 mg. The second (12-) had a prolonged hospitalization for a seizure three days after starting atorvastatin and was dropped from the study. The seizure was not considered related to atorvastatin. A third patient developed fatigue, bloating, swelling of the thighs and upper arms, and pruritis after 3 days of therapy with atorvastatin 40 mg. Symptoms resolved after discontinuation of study medication and the patient was dropped from the study.

No patients had a clinically important elevation in ALT, AST, or CK as of March 31, 1996.

Lp(a):
No Lp(a) measurements are included in the study report.

Labeling issues
Though the experience in FH homozygotes is limited to 30 patients total to date (8 patients in 981-54, 22 new patients in 981-80), the efficacy in all but five of those patients is evident. These data support a claim for the use of atorvastatin as an adjunct to other treatment modalities in homozygous FH.

Table 7.5.7. 981-80: Results at week 8 or highest titration

Patient ID	Phenotype	Age	Maximum Atorvastatin Dose (mg)	Baseline LDL-C (mg/dL)	Change in Lipid Parameters				Comments
					LDL-C	TC	TG	HDL-C	

Patient ID	Phenotype	Age	Maximum Atorvastatin Dose (mg)	Baseline LDL-C (mg/dL)	Change in Lipid Parameters				Comments
					LDL-C	TC	TG	HDL-C	

LDL-C = Low-density lipoprotein cholesterol.
TC = Total cholesterol.
TG = Triglycerides.
HDL-C = High-density lipoprotein cholesterol.
N/A = Not available.

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7.6 Effect of atorvastatin in patients with NIDDM and in postmenopausal women

Atorvastatin in NIDDM

Hypercholesterolemia is a risk factor for CHD in patients with and without diabetes. In the latter group, hypercholesterolemia is often more difficult to treat. Diabetes associated dyslipidemias are often further characterized by elevated triglyceride due to increased hepatic TG and VLDL production. Of the available treatment options, most are either ineffective or associated with serious adverse metabolic effects. Bile acid binding resins tend to raise TG levels in NIDDM and niacin impairs glycemic control by augmenting insulin resistance. While well tolerated, fibric acid derivatives have their principal impact on TG and on raising HDL-C, with little effect on lowering LDL-C.

The sponsor conducted studies on the effects of atorvastatin in NIDDM complicated by hypercholesterolemia in order to demonstrate the efficacy and safety of the drug in this group of patients at increased risk for CHD.

This section will briefly review the findings of two clinical trials in patients with hypercholesterolemia and NIDDM, one a small pilot study, the second a follow up study to further characterize the comparative effects of simvastatin and atorvastatin in this patient population. Finally, the analysis by the sponsor of pooled data on the effects of different doses of atorvastatin on lipid parameters in patients with NIDDM will be reviewed.

Study 981-13

Design

This was a 4-week, open-label, comparative study of atorvastatin and simvastatin, both at a dose of 10 mg, in 25 patients, mean age 61 years. 13 men and 12 women with NIDDM stabilized on hypoglycemic agents and with LDL-C >160 mg/dl were randomized (13 Atorvastatin, 12 simvastatin). One atorvastatin patient was withdrawn after 2 weeks when it was discovered he did not meet the lipid entry criteria.

Treatment groups were well matched at baseline for age, gender, BMI, fasting glucose, Hg A1c, fructosamine, and fasting insulin. Mean (SE) LDL-C was 187 (8) in the atorvastatin group and 206 (8) in the simvastatin group. Mean (SE) TG was 194 (18) in the atorvastatin patients and 203 (36) in the simvastatin group.

After a 4-week dietary baseline period, patients were treated with either simvastatin 10 mg or atorvastatin 10 mg for 4 weeks, with clinic visits every 2 weeks for laboratory and clinical monitoring and dietary instruction.

Baseline was the mean of determinations at weeks -2 and 0 and results were analyzed by intent to treat. Comparison of differences between treatment groups in percent change from baseline was made by analysis of covariance with a model including effects of treatment, center, and with baseline as a covariate.

Both treatments lowered total, LDL-C, VLDL-C, and TG from baseline, with atorvastatin

statistically significantly superior to simvastatin for these parameters. The table below summarizes the unadjusted means and standard errors for these measures.

Table 7.6.1. 981-13: Percent reduction from baseline in lipid parameters after 4 weeks of therapy

	Total C	LDL-C	TG	VLDL-C
Ator 10mg	-30 (3)	-39 (4)	-27 (6)	-41
Simva 10 mg	-24 (1)	-30 (2)	-15 (4)	-32

Glycemic parameters and insulin levels did not change significantly in either group.

Adverse events
In the atorvastatin group, two patients experience myalgias, one with mildly elevated CPK. A third patient complained of constipation. In the simvastatin group, one patient developed myalgia with normal CPK.

Study 981-47
Based on the results of the preceding study, a larger, longer-term, double-blind study was conducted to compare the effects of simvastatin and atorvastatin in patients with NIDDM and hypercholesterolemia with and without hypertriglyceridemia.

Design:
Men and women aged 35 to 80 years eligible for inclusion had NIDDM defined as plasma glucose (PG) >200 mg/dl or fasting PG >140 mg/dl on 2 occasions, or fasting PG >140 mg/dl and 2 positive oral glucose tolerance tests. Glycemic control with glycosylated hemoglobin <15% was required. Lipid entry criteria were LDL>130 and TG between 150 and 600, all at weeks -4 and -2.

After a 6-week placebo and dietary baseline phase, patients were randomized to treatment with either simvastatin 10 mg or atorvastatin 10 mg and LDL-C goals of <100 and <130 were set based on presence or absence of a history of CHD, respectively. After 4 weeks of treatment, those patients not reaching LDL-C goals were to have the dose of drug doubled for the remainder of the 26 week study.

166 patients were randomized (84 atorvastatin, 82 simvastatin). Treatment groups were well matched at baseline for age, gender, lipids, and CHD risk status. About 25% of each group had a history of CHD. Mean age was 63. 62% of each group were female. Means for LDL-C at baseline were 175 mg/dl and 181 mg/dl in the atorvastatin and simvastatin groups, respectively. TG means were 299 and 290, respectively.

Both drugs were effective in lowering LDL-C from baseline. At the end of week 4, 67% of atorvastatin patients had reached LDL-C goal and 53% of simvastatin patients had reached goal. After dose escalation and at the end of 26 weeks, 46% of patients on atorvastatin 20 as compared to 26% of those on simvastatin 20 had reached goal.

At the end of 26 weeks, adjusted mean reduction in TG was 24% for the atorvastatin group and

15% for the simvastatin group. The week 26 efficacy results are summarized in the table below.

Table 7.6.2. 981-47: Efficacy results at week 26

Parameter % change (SE)	Ator 10-20 N=84	Simva 10-20 N=81
LDL-C	-34 (1.7)	-31 (1.6)
HDL-C	12 (2)	11 (1.9)
TG	-24 (3.8)	-15 (3.7)
non-HDL/HDL-C	-38 (1.8)	-34 (1.7)

Safety

The safety profiles of the two drugs were similar in this study. There were no serious adverse events considered related to study drugs. 2 atorvastatin and 4 simvastatin patients withdrew due to adverse events. Of these 6, one atorvastatin patient had abdominal pain and another myalgia, and three simvastatin patients had GI disorders considered related to drug. One patient had an asymptomatic elevation in CPK to >10 x ULN (level= 10,000 U/L) and AST > 3 x ULN (211 U/L) on the last day of the study that resolved on discontinuation of drug. Rechallenge over 6 months in an extension study resulted in 2 isolated mild elevations in CPK that have resolved spontaneously. AST has remained normal.

Pooled data analysis

The sponsor performed an analysis of the effect of atorvastatin at 10 mg and 80 mg/day on patients with and without NIDDM is a database pooled from all the clinical studies in the NDA of parallel-group design, thus excluding the 92 patients in study 981-07 (crossover). This analysis, summarized in the table below, reproduced from the integrated summary of effectiv[illegible] clearly demonstrates the parallel effectiveness of atorvastatin in both types of patients.

TABLE 7.6.3. Efficacy of Atorvastatin Treatment in Patients With NIDDM* and Without NIDDM: Pooled Studies Dataset

[Mean Percent Change (SE)]

Lipid Parameter	Atorvastatin Dose															
	10 mg				20 mg				40 mg				80 mg			
	NIDDM N = 156		Non-NIDDM N = 1329		NIDDM N = 8		Non-NIDDM N = 139		NIDDM N = 1		Non-NIDDM N = 73		NIDDM N = 4		Non-NIDDM N = 314	
All Patients																
LDL-C	-36	(1)	-35	(<1)	-44	(4)	-43	(1)	-33	-47	(1)		-59	(4)	-53	(1)
Apo B	-29	(1)	-28	(<1)	-32	(4)	-29	(2)	-29	-40	(1)		-51	(4)	-45	(1)
Total C	-27	(1)	-27	(<1)	-33	(2)	-33	(1)	-27	-35	(1)		-47	(5)	-43	(1)
TG	-21	(2)	-17	(1)	-1	(15)	-18	(3)	-36	-23	(3)		-11	(14)	-31	(1)
VLDL-C	-29	(3)	-19	(1)	not done		-42	(4)	not done	-41	(9)		-20	(15)	-33	(2)
HDL-C	+9	(1)	+7	(<1)	+4	(5)	8	(1)	7	9	(1)		-11	(4)	7	(1)
Non-HDL-C/ HDL-C	-37	(1)	-37	(<1)	-41	(5)	-43	(1)	-38	-47	(1)		-48	(7)	-53	(1)
Apo B/HDL-C	-33	(1)	-32	(<1)	-35	(5)	-32	(2)	-35	-42	(2)		-45	(4)	-47	(1)

* Patients in Studies 981-13 and 981-47, who were receiving concurrent treatment for NIDDM, or had glucose > 160 mg/dL

Conclusions

In sum, though the number of patients studied was relatively small, and virtually all were treated with 10 mg, the efficacy of atorvastatin in patients with NIDDM has been demonstrated. Within the limits of the data, there are no apparent safety issues peculiar to patients with NIDDM. Clearly, though, the possibility of drug-drug interactions is heightened in patients with concurrent medical conditions taking multiple medications. No specific claims are made in the proposed label addressing the efficacy of atorvastatin in patients with NIDDM.

Atorvastatin in postmenopausal women

Study 981-12
The risk of CHD increases in postmenopausal women, generally felt, in part, to be a function of changes in plasma lipoproteins that result from estrogen deficiency. Though estrogen replacement therapy can result in lower LDL-C and increases in HDL-C, in some patients it may be contraindicated or inadequate therapy for dyslipidemia. Furthermore, estrogens can exacerbate hypertriglyceridemia in predisposed individuals.

The present study was undertaken to test the effectiveness of atorvastatin as compared to estrogen and to combination atorvastatin and estrogen therapy in postmenopausal females with moderate hypercholesterolemia with or without hypertriglyceridemia.

Design
After a 6-week dietary and placebo baseline run-in, 86 women, with a mean age of 61 years and LDL-C>145 mg/dl on diet were randomized to receive placebo (N=23), atorvastatin 10 mg (N=20), estradiol 1 mg (N=17), or the combination of the latter two (N=23). After 12 weeks, the placebo patients were switched to atorvastatin and the trial was continued for another 40 weeks.

The treatment groups were well matched at baseline for age, BMI, Fredrickson type, LDL-C, and TG. The mean LDL-C for the overall study population was 191 mg/dl.

Results
Results at both weeks 12 and 52 showed that 10 mg atorvastatin was significantly better than estradiol in lowering LDL-C, TG, as well as the ratio of non-HDL-C to HDL-C, while the combination of atorvastatin plus estradiol resulted in the greatest increase in HDL-C. The 52-week results are shown in the table.

Safety
With regard to safety, for the 52 weeks of the study, overall adverse events were more common in the estradiol and atorvastatin plus estradiol groups than for the atorvastatin alone groups. Fewer atorvastatin patients had adverse events considered related to drug than did in the other two active treatment groups. The most frequent adverse events felt associated with atorvastatin therapy were headaches, dyspepsia, and abdominal pain, all in 5% of patients. There were no serious adverse events considered related to drug in any of the treatment groups. There were no deaths in the study. There were no clinically significant lab abnormalities. 30% of atorvastatin patients had at least one abnormal laboratory test, with ALT and AST >ULN and less than 3 x ULN being the most common abnormality.

TABLE 7.6.4. Summary of the Primary and Secondary Efficacy Parameters at Week 52: Mean (Standard Error)

Parameter	Combined Atorvastatin (10 mg)*		Placebo + Estradiol (1 mg)		Atorvastatin (10 mg) + Estradiol (1 mg)	
Primary Efficacy Parameter						
LDL-C (Friedewald)						
N	38		16		21	
Baseline (mg/dL)	197	(5.7)	187	(6.3)	191	(5.5)
Last Visit (mg/dL)	119	(5.9)	176	(6.7)	110	(4.0)
Change (mg/dL)	-78	(4.5)	-12	(3.1)	-80	(4.3)
Adj % Change	-40	(2.1)	-5*	(2.8)	-42	(2.3)
Secondary Efficacy Parameters						
Total Cholesterol						
N	38		16		21	
Baseline (mg/dL)	287	(6.7)	273	(7.7)	279	(6.8)
Last Visit (mg/dL)	205	(7.4)	271	(7.5)	205	(5.1)
Change (mg/dL)	-82	(5.0)	-2	(3.4)	-74	(4.8)
Adj % Change	-29	(1.8)	-1*	(2.4)	-27	(1.9)
HDL-C						
N	38		16		21	
Baseline (mg/dL)	52	(1.7)	50	(1.6)	52	(2.1)
Last Visit (mg/dL)	57	(1.7)	56	(2.5)	62	(2.7)
Change (mg/dL)	4	(0.9)	6	(2.2)	10	(1.6)
Adj % Change	8	(2.8)	11	(3.9)	20*	(3.1)
VLDL-C						
N	38		16		21	
Baseline (mg/dL)	38	(3.2)	37	(3.0)	38	(3.8)
Last Visit (mg/dL)	27	(2.8)	42	(4.3)	32	(3.8)
Change (mg/dL)	-12	(2.0)	5	(3.4)	-6	(2.3)
Adj % Change	-32	(6.2)	13*	(8.5)	-20	(6.9)
Triglycerides						
N	38		16		21	
Baseline (mg/dL)	186	(13.4)	179	(13.6)	181	(17.0)
Last Visit (mg/dL)	148	(13.2)	197	(15.7)	162	(17.6)
Change (mg/dL)	-38	(6.6)	18	(10.0)	-19	(12.1)
Adj % Change	-27	(4.5)	5*	(6.3)	-13*	(5.1)
Lp(a)						
N	38		16		21	
Baseline (mg/dL)	37	(6.1)	46	(15.1)	54	(10.5)
Last Visit (mg/dL)	38	(6.7)	41	(14.3)	56	(12.7)
Change (mg/dL)	2	(1.2)	-5	(2.6)	3	(5.0)
Adj % Change	-8	(5.6)	-28*	(7.8)	-10	(6.3

Adjusted mean percent changes are based on an ANCOVA model with effects due to treatment, center, and baseline.

* Significantly different from atorvastatin, $p \leq 0.05$

* Atorvastatin treatment group combined with those patients who were switched from placebo in Period 1 to atorvastatin in Period 2

Discussion

No specific claims are made in the proposed label with regard to the efficacy of atorvastatin in postmenopausal women. Within the limits of the scope of a small study, there appear to be no safety issues peculiar to this group of patients. It is interesting to note that in drug interaction

studies, atorvastatin coadministered with oral contraceptives increased AUC values for synthetic estrogens by 20-30%. The apparent synergistic effect of atorvastatin and estradiol on HDL-C may actually reflect a greater exposure to estradiol. The long term effects of such increased exposure, if it indeed occurs, on liver, breast, uterus are not clear.

7.7 Study 981-48: Effect of atorvastatin 80 mg on hemorrheology

In addition to the direct effects on the vascular endothelium and arterial wall, excess plasma lipids are associated with abnormalities in red blood cell deformability, increases in plasma viscosity, alterations in platelet aggregability, all contributing to the risk of arterial (and in some instances, venous) thrombosis. Previous research has demonstrated improvements in hemorrheological parameters with pharmacologic lipid lowering. The current study investigated the effects of atorvastatin 80 mg on plasma viscosity and other parameters in 22 patients with hypercholesterolemia (Types II a, II b, and IV).

Design
This was a 12-week, open-label study in 22 men, without serious concomitant illness, non-smoking, non-alcohol abusing with Type IIa (N=8), Type IIb (N=8), and Type IV (N=6) hyperlipoproteinemia. Lipid entry criteria were for Type IIa, LDL-C>160 and TG <200; for Type IIb, LDL-C >160 and TG between 200 and 650; for Type IV, LDL-C <160 and TG between 300 and 650. The mean age was 48 years. Mean LDL-C was 172 (range 70-309). Mean TG was 262 (range 80-605). Mean Lp(a) was 23 (0-81).

After a minimum 2-week dietary lead in phase, patients entered a 6- week placebo baseline period. Following this, patients were treated for 12 weeks with atorvastatin 80 mg and followed by history, physical, and laboratory testing at 4-week intervals. Baseline hemorrheological parameters were the mean of two determinations at the end of the placebo period. Hemorrheologic parameters were also measured twice at the end of the treatment phase and the mean of these two determinations served as the value in response to treatment.

Results
The primary endpoint was the percent change from baseline in plasma viscosity. All other parameters were analyzed as secondary endpoints. Results are presented in the study report for all patients combined and by Fredrickson phenotype. For the most part, trends were similar in the individual subgroups. The analyses for all patients combined will be the focus of this review.

Changes from baseline in lipid parameters (TC, TG, LDL-C, VLDL-C, HDL-C) were all consistent with the results of previous studies reviewed here. For all patients combined, the mean percent change from baseline in LDL-C was -53%.

The table below summarizes the hemorrheological changes following 12 weeks of therapy for all patients combined.

Table 7.7.1. Study 981-48: Hemorrheological parameters

	All patients (N=22)	
Parameter	Baseline value	% change from baseline
Plasma viscosity	2	-10*
Fibrinogen	316	1
t-PA antigen	20	-1
ADP-induced plt aggreg	9	3
AA-induced plt aggreg	16	-11*
collagen-induced aggreg	20	6
hematocrit	43	-1
PAI-1 activity	10	5
factor VII activity	114	-8*
RBC deformability	113	-2
RBC lipid ratio	0.8	5*
RBC sedimentation	10	-33*
Lp(a)	23	36*

AA=arachidonic acid; PAI-1=plasminogen activator inhibitor
* significantly different from baseline,$p<0.05$

At the end of 12 weeks, there were reductions in several parameters that were significant, including plasma viscosity, arachadonate-induced platelet aggregation, factor VII activity, and red blood cell sedimentation. These and other trends were consistent across Fredrickson phenotypes.

As was seen in the pilot study in FH homozygotes (study 981-54), Lp(a) was significantly increased in the overall study group by 36%. In none of the individual Fredrickson phenotype subgroups did the change reach statistical significance, though all groups showed increases, with a 50% change from baseline in the Type IIb patients. Again, as in the FH patients, the clinical significance of this finding is not known, though based on epidemiologic data, the concern is that this change might offset other apparent benefits of the drug.

Conclusions/labeling:
No specific reference is made to the results of this study in the proposed label.

7.8 Efficacy of atorvastatin in subsets of the pooled study population

Introduction

This final section of the review of efficacy of atorvastatin encompasses the sponsor's analyses in the Integrated Summary of Effectiveness of outcomes in response to atorvastatin in subsets of the pooled study population. A description of these analyses is relevant to claims made in the proposed package insert for atorvastatin. Furthermore, pooling of response data across the multiple studies included in this NDA is without question a valid analytical strategy. It is justified by the fact that, to begin with, most protocols shared the feature of a diet and placebo run-in with dietary instruction and compliance monitoring throughout follow-up. In addition, study populations were fairly consistent in age, gender, and race make-up. This, in conjunction with the fact that, historically as well as in this database, there is no significant placebo effect in the treatment of the hyperlipoproteinemias, allows for pooling and direct comparisons across studies of individual and mean changes from baseline in lipid parameters.

As described previously, the data from atorvastatin-treated patients were pooled from all the clinical studies of parallel-group design (thus excluding the 92 patients in 981-07). This was a total of 2077 patients, 1367 with Fredrickson Type IIa, 657 patients with Type IIb, and 53 patients with type IV. Efficacy data were obtained from fixed-dose studies at the end of treatment and from dose-titration studies before the target-based titration. Most of the Type IIa/IIb (1485/2024) patients received 10 mg atorvastatin.

The purpose in pooling the data was to provide additional information about the effect of atorvastatin by Fredrickson phenotype, by genotype (FH versus non-FH), in patients with NIDDM, by age, gender, and race. In addition, the analyses explored the effect of concurrent disease, history of hypertension, altered renal or hepatic function, and previous HMGRI use on the response to atorvastatin. Safety in these same subgroups will be addressed later in the review.

Efficacy by Phenotype

Patients treated with atorvastatin in the pooled studies dataset were categorized by baseline LDL-C and TG values (to separate Fredrickson phenotypes), and by whether or not they had FH or NIDDM. Most patients (935/1485) treated with 10 mg atorvastatin were of the Fredrickson Type IIa phenotype (primary hypercholesterolemia).

The effect of 10 mg of atorvastatin in lowering LDL-C, apo B, and total cholesterol was similar in Type IIa and Type IIb patients. Type IIb patients experienced a greater percent decrease in TG and VLDL-C levels compared with Type IIa patients, which is consistent with higher TG and lower LDL-C levels at baseline. The results are summarized in the table below.

TABLE 7.8.1. Efficacy of Atorvastatin 10 mg by Fredrickson Type: Pooled Studies Dataset [Mean (SE)]

Lipid Parameter	Type IIa N = 935		Type IIb N = 550		Type IV N = 29	
LDL-C						
Baseline, mg/dL	195	(0.9)	193	(1.4)	118	(2.7)
Percent Change	-36	(<1)	-35	(1)	-26	(3)
Apo B						
Baseline, mg/dL	162	(1.0)	177	(1.3)	130	(3.4)
Percent Change	-28	(<1)	-28	(1)	-25	(2)
Total Cholesterol						
Baseline, mg/dL	273	(1.0)	290	(1.5)	245	(5.5)
Percent Change	-27	(<1)	-27	(<1)	-25	(2)
TG						
Baseline, mg/dL	133	(1.2)	284	(3.5)	506	(39.1)
Percent Change	-14	(1)	-24	(1)	-29	(5)
VLDL-C						
Baseline, mg/dL	26	(0.3)	56	(0.8)	95	(7.3)
Percent Change	-15	(1)	-28	(1)	-41	(4)
HDL-C						
Baseline, mg/dL	51	(0.4)	42	(0.4)	33	(1.3)
Percent Change	+6	(<1)	+10	(1)	+13	(4)
Apo B/HDL-C						
Baseline, mg/dL	3.1	(0.03)	4.2	(0.06)	4.2	(0.18)
Percent Change	-31	(<1)	-34	(1)	-33	(2)
Non-HDL-C/HDL-C						
Baseline, mg/dL	4.6	(0.04)	6.2	(0.07)	6.9	(0.37)
Percent Change	-37	(<1)	-38	(1)	-38	(2)

Although there were only 29 patients with Type IV hyperlipoproteinemia treated with atorvastatin 10 mg in the dataset, nevertheless, as discussed in an earlier section, the drug was clearly effective in lowering LDL-C Apo B, and TC. Additionally, of significance was the marked effect on TG and VLDL-C in these patients.

Labeling

These and other data presented establish the drug's effectiveness in primary hypercholesterolemia, mixed dyslipidemia, and as a viable alternative to usual therapies in the treatment of isolated hypertriglyceridemia.

Efficacy in Type IIa and IIb patients with and without FH (heterozygous):

When the effect of atorvastatin was examined in Type IIa and IIb patients by hypercholesterolemia genotype (FH versus non-FH), again in keeping with the findings of individual studies, the pooled data revealed a remarkable consistency in mean percent reduction in LDL-C, TC, Apo B, and non-HDL-C/HDL-C from baseline in both subgroups. The vast majority (~90%) of the patients receiving atorvastatin 10 mg had non-FH hypercholesterolemia. However, despite limited data in heterozygous FH, in both groups, atorvastatin 10 mg effected a mean reduction in LDL-C of about 35% while the mean reduction in LDL-C in response to atorvastatin 80 mg in both groups was between 51 and 58%.

When subgroup analysis was performed by NIDDM versus non-NIDDM, again for the Type IIa and IIb patients, the consistency of the atorvastatin effect in altering lipids reconfirms the conclusions from the individual studies of effects of the drug in hypercholesterolemia with concurrent NIDDM. The table below summarizes the data for LDL-C.

TABLE 7.8.2. Efficacy of Atorvastatin on LDL-C By Hypercholesterolemia Phenotypes [Mean % Change (SE)]

Phenotype	10 mg Atorvastatin			80 mg Atorvastatin		
	N	LDL-C		N	LDL-C	
FH						
Homozygous	none		–	8	-31	(4)
Heterozygous	140	-36	(1)	154	-53	(1)
IIa	80	-37	(1)	117	-54	(1)
IIb	60	-35	(2)	37	-51	(2)
Non-FH						
NIDDM	159	-35	(1)	3	-57	(4)
IIa	52	-35	(2)	2	-56	(7)
IIb	99	-36	(1)	1	-58	–
IV	8	-30	(6)	none		--
Non-NIDDM	1215	-36	(<1)	166	-52	(1)
IIa	803	-36	(<1)	104	-55	(1)
IIb	391	-34	(1)	49	-53	(2)
IV	21	-24	(3)	13	-35	(6)

Efficacy by Age

The effect of atorvastatin treatment on LDL-C lowering was compared in younger (<70 years) and older (>70 years) patients. Eighty-nine percent (1803/2024) of Fredrickson Types IIa and IIb patients were <70 years of age. This age distribution was consistent between genders with 92% (1021/1109) of the treated men and 85% (782/915) of the treated women <70 years of age.

TABLE 7.8.3. Efficacy in Older and Younger Patients by Dose: Pooled Studies Dataset (Fredrickson Types IIa and IIb)
[Mean (SE) LDL-C]

Atorvastatin Dose	Patients			
	<70 years		≥70 years	
10 mg, N	1302		183	
Baseline, mg/dL	194	(0.8)	192	(2.0)
% Change	-35	(<1)	-39	(1)
20 mg, N	126		21	
Baseline, mg/dL	211	(2.2)	217	(5.8)
% Change	-44	(1)	-37	(5)
40 mg, N	69		5	
Baseline, mg/dL	197	(4.8)	177	(5.2)
% Change	-47	(1)	-52	(6)
80 mg, N	306		12	
Baseline, mg/dL	270	(4.1)	211	(16.6)
% Change	-53	(1)	-61	(2)
All Doses, N	1803		221	
Baseline, mg/dL	209	(1.2)	195	(2.0)
% Change	-39	(<1)	-40	(1)

The results demonstrate that for patients greater than or less than 70 years of age, the LDL-C-lowering efficacy of atorvastatin increases with increasing dose. In addition, there appears to be some trend toward an increased effect of atorvastatin in older patients, most pronounced at the 80-mg dose with a mean 53% reduction in LDL-C in the <70 group and a mean 61% reduction in the >70 group. According to the sponsor, the effect of age on LDL-C lowering is statistically significant. While these differences in mean percent reduction in LDL-C are unlikely to be of clinical significance, they perhaps reflect the increased Cmax and AUC observed in pharmacokinetic studies in elderly patients. To the extent that for equivalent doses, elderly patients may have a more marked therapeutic response, the obvious concern arises that they might also be more prone to adverse reactions (e.g. liver, muscle). This concern is not borne out by the data in this NDA.

Efficacy by gender
There were no differences in the response to atorvastatin between the sexes across the dosage range proposed for marketing. Data from 1109 men and 915 women (55:45) were analyzed in the pooled dataset.

Efficacy by menopausal status
There were no clinically meaningful differences in the overall response to atorvastatin between

pre- and post-menopausal women in the pooled dataset. 83% of the women in these trials were post-menopausal.

Efficacy by race

In the pooled studies dataset, 10 mg was the only atorvastatin dose for which there were sufficient non-white patients to make comparison. When the efficacy in the 100 non-white patients receiving 10 mg was compared to that in whites, the results were similar for all parameters examined.

It is perhaps interesting to note at this point that data from a small 8-week, double-blind, placebo-controlled dose-ranging study in 119 Japanese patients (efficacy data in 107) show that over the dose range studied (5, 10, and 20 mg), the response with regard to reduction in LDL-C was greater than what has been observed in the other trials in this NDA. Patients with mean baseline LDL-C in the range of 220-240 showed percent reduction from baseline in LDL-C of 36, 41, and 50% at doses of 5, 10, and 20 mg, respectively. No other efficacy data from this study are included in the NDA.

Efficacy by concurrent disease

When the population that received atorvastatin 10 mg was categorized by whether or not the patients were on concurrent antihypertensive medication, the was no difference in the response for the lipid parameters measured.

Efficacy by altered renal function

Subdividing the 10 mg atorvastatin group by baseline BUN or creatinine value greater than or less than 1.25 times the ULN showed no differences in effect of drug on lipid parameters of mild alteration in renal function.

Efficacy by altered hepatic function

Subdividing the 10 mg atorvastatin group by baseline ALT or AST greater than or less than 1.25 times the ULN showed no differences in effect of drug on lipid parameters as a function of mild alteration in hepatic function.

Efficacy by previous HMGRI experience

As patients with previous exposure to HMGRIs were not excluded from the clinical trials in this NDA, the sponsor subdivided the 10 mg atorvastatin group by whether or not the patients had ever been treated with HMGRIs. 26% had previous exposure. No difference in the efficacy of the drug in these two subgroups was evident. Thus, this was not a source of bias in the database.

Discussion/labeling
No specific efficacy claims relating to the analyses above are made in proposed labeling.

Section 8
Safety review

Introduction
The section of the NDA review devoted to the safety of atorvastatin will include an overview of the safety profile of the drug with regard to overall adverse events compared to placebo and to other lipid altering agents used in trials submitted to the NDA. In addition, the deaths, serious adverse events, and dropouts catalogued will be reviewed. The emphasis will be on the data from the clinical studies. The comparative safety of amorphous and crystalline atorvastatin will also be addressed. The four-month safety update is reviewed separately at the end of the section. This includes up to two years of follow up of patients on atorvastatin as well as a safety comparison of 80 mg crystalline atorvastatin and 80 mg amorphous atorvastatin.

The main focus of the safety review will be on the profile of atorvastatin with regard to those adverse effects either known to be or theoretically associated with members of the HMGRI class (the statins). These include effects on liver function manifest as elevations in hepatic enzymes, on muscle with attendant elevations in CK, on the lens of the eye, and on adrenal function. No studies specifically examined the effect of atorvastatin on coenzyme Q levels or on testicular function. There were no specific safety issues raised in the database with regard to demographic groups (age, gender, race), interactions with other drugs, or with underlying disease states.

8.1 Data groupings within the clinical studies database
For the purposes of summarizing information from the completed studies, he sponsor has pooled safety data in several ways. I will briefly describe these data groupings and the rationale behind them. The drug exposures in each of these groupings will also be summarized. In the discussion of specific safety issues, I will refer to one or more of the groupings to illustrate particular points.

Safety information in the integrated database for the 21 completed clinical studies was evaluated by the sponsor for 4 separate data groupings or subsets: **All Completed Studies** (N = 2502 atorvastatin-treated patients), **Placebo-Controlled Studies** (N = 1122 atorvastatin-treated patients), fixed-dose portion of all studies termed **Fixed-Dose** (N = 2275 atorvastatin-treated patients), and **1-Year Studies** (N = 1545 atorvastatin-treated patients). These data groupings are not mutually exclusive; therefore, patients are included in more than 1 data grouping. The table below summarizes the characteristics of the data groups.

TABLE 8.1.1. Database Groupings

Data Grouping	Studies Included in Data Grouping	Number of Patients Who Received Atorvastatin	Purpose
Placebo-Controlled Studies	4, 8, 10, 12, 25, 38, 96	1122[a]	Dose-response evaluation and placebo-comparison with data from studies with parallel, placebo-treatment arms
Fixed-Dose Portion of All Studies (Fixed-Dose)	4, 7, 8, 9, 10, 12, 13, 14, 25, 37, 38, 42, 43, 44*, 47, 48*, 54*, 55, 56, 57, 96	2275[b]	Dose-response evaluation with data from all studies with only data from Period 1 of studies in which dose titrated or treatment changed and comparison with other HMGRIs or other lipid-lowering agents
1-Year Studies	8, 9, 12, 37, 56, 57	1545[c]	Long-term safety with data from controlled studies of a year's duration
All Completed Studies	4, 7, 8, 9, 10, 12, 13, 14, 25, 37, 38, 42, 43, 44*, 47, 48*, 54*, 55, 56, 57, 96	2502[d]	Overview of safety across all studies of various design (placebo-controlled, active-controlled, an uncontrolled) and duration

* Uncontrolled studies.

[a] For Studies 981-008 and -012, includes data from only the placebo-controlled, fixed-dose/treatment portion (Period 1). From Studies 981-007, -008, -009, -012, -037, -047, -055, -056, and -057 includes data only from Period 1. Atorvastatin treatment group contains data for 23 patients who received atorvastatin plus estradiol in Study 981-012 and 20 patients who received atorvastatin plus colestipol in Study 981-043.

[b] Atorvastatin treatment group contains data for 23 patients who received atorvastatin plus estradiol throughout Study 981-012.

[c] Included in atorvastatin treatment group are data for patients who received placebo in Period 1 of Studies 981-008 and 981-012; patients who received estradiol and atorvastatin combination therapy in Study 981-012; patients who received atorvastatin plus colestipol in Study 981-043; and patients who received colestipol in Period 1 of Study 981-056, then changed to atorvastatin and colestipol in Period 2.

The **Placebo-Controlled Studies** subset contains data from 7 clinical studies, including 2 studies in which only data from the placebo controlled periods were included This data grouping allowed for an evaluation of any dose-related effects of atorvastatin in comparison with placebo, with data from studies in which mean exposure within each study to both placebo and active treatment would be similar. The duration of exposure to atorvastatin in these studies was from 4 weeks to 6 months.

The **Fixed-Dose** subset includes data from all study designs: placebo-, active-, and un-controlled. Data from only the fixed-dose or treatment portions (Period 1) of the studies was included. This data grouping enabled a comparison of atorvastatin's effects with those of other HMGRIs, as well as other types of lipid-lowering agents, before treatment or dose change in titration studies. Exposure to atorvastatin was from 4 to 16 weeks. Little exposure was at the higher doses (40 and 80 mg).

The **1-Year Studies** subset was chosen to provide an evaluation of long-term safety among patients who had participated in controlled studies of a year's duration. This data grouping comprises the majority of all safety data in the integrated database. It was selected for homogeneity in study design and duration of treatment.

The **All Completed Studies** dataset provides a general and complete overview of safety across the 21 completed studies for all the patients exposed to atorvastatin in clinical studies. As such, it includes data from individual patients from time periods on placebo and on different doses atorvastatin, on comparator agents, and on combination therapy.

Ongoing studies:

Safety data from ongoing studies will be summarized in the 4-month safety update for this NDA.

8.2 Exposure (scope of the safety database):

The table below summarizes the total exposure to atorvastatin in the safety database as of March 15, 1996, excluding that in ongoing trials.

Table 8.2.1. Numbers of patients receiving atorvastatin in Clin Pharm and Clinical Studies

STUDIES	NUMBER OF PATIENTS:
Clinical Pharmacology Studies	590
Clinical Studies	2502

In addition, 119 patients were treated in a single study conducted in Japan the results of which were mentioned briefly in the efficacy review. The total exposure in the clinical pharmacology studies was 8390 subject-days and in clinical studies was 1845 patient years.

Exposure to atorvastatin in clinical trials

Exposure by data subsets
The number of patients and total exposure in the four clinical data subsets are summarized below.

Table 8.2.2. Exposure in safety data subsets

Data subset	Number of patients	Patient-years exposure
Placebo-controlled	1122	342
Fixed-dose	2275	634
1-year studies	1545	1447
All-completed	2502	1845

Exposure by dose of atorvastatin in the different datasets
In the **placebo-controlled** data subset, the greatest exposure was to atorvastatin 10 mg (863 patients, 294 patient-years). All told, 63% of the patients took atorvastatin for at least 4 months. Exposure to 80 mg was 20 patient-years. This dataset does not include any of the patients exposed to 80 mg atorvastatin in 52-week trials.

Table 8.2.3. Placebo-controlled grouping

Dose	N	Patient-years exposure
Placebo	270	~80
10 mg	863	294
20 mg	36	4
40 mg	79	20
80 mg	94	20
All atorvastatin	1122	342

In the **fixed dose** data subset, 48% of the patients took atorvastatin for at least 4 months, again with the greatest exposure at the 10 mg dose (487 patient-years). This dataset includes less than half of the 80 mg exposure in the database, which is restricted to shorter term (≤16 weeks) exposures, and all of the placebo exposure.

Table 8.2.4. Fixed-dose grouping

Dose	N	Patient-years exposure
Placebo	270	~80
10 mg	1589	487
20 mg	189	30
40 mg	79	20
80 mg	345	91
All atorvastatin	2275	634
Other HMGRIs	539	142

In the **1-year studies** data subset, 90% of patients took atorvastatin for at least 11 months and 70% for at least 1 year.

Table 8.2.5. 1-years studies grouping

Treatment	N	Patient-years exposure
Atorvastatin	1545	1447
Other HMGRIs	389	363
Estradiol	19	16

In the **all-completed studies** subset, for the 2502 atorvastatin-treated patients, the distribution of patients by duration of exposure is summarized in the table.

Table 8.2.6. All completed studies

Minimum duration of exposure	Number of patients (%)
4 weeks	2453 (98)
8 weeks	2228 (89)
16 weeks	1835 (73)
6 months	1721 (69)
1 year	1253 (50)

The exposure by dose in the **all-completed studies** dataset is shown in the table. The total number of patients exceeds the 2502 because of inclusion of data from dose titration studies in which patients changing dose are counted more than once.

Table 8.2.7. All completed studies

Dose (mg/day)	Number of patients	Exposure (patient-years)
2.5	11	1
5	49	6
10	1677	1083
20	753	301
40	493	157
60	13	2
80	383	222

In this dataset, most of the exposure was in the 10 mg group, in which over 750 patients were exposed for 1 year. About 100 patients were exposed to 20 mg/day for 1 year, and fewer than 50 were treated with 40 mg/day for 1 year. About half of the patients who received 80 mg/day in clinical trials received that dose for nearly one year in study 981-56, all told about 200 individuals. It is thus clear that the **all completed studies** safety database is weighted toward the 10 mg dose of atorvastatin, which accounted for nearly 60% of the total exposure. It is also important to realize that the bulk of the exposure to both 10 and 80 mg is in patients treated for 1 year. As such, then, with regard to duration of treatment in individual patients, and adverse reactions related to cumulative exposure, these two treatment groups are better compared to one another than to the other dosage groups, where the percentage of patients receiving drug over longer periods was relatively small. Finally, for purposes of comparison, the exposure to the other HMGRIs was also in 1-year studies.

8.3 Adverse events

Clinical pharmacology studies

The demographic characteristics of the Clinical Pharm study population were similar to those of the overall population in the clinical studies. As the adverse event experience in the clinical pharmacology studies was not substantively different from that in the clinical studies, the detailed discussion of atorvastatin-associated adverse events will be restricted to the clinical studies. In short, in the clinical pharmacology studies, fifty-six percent of subjects reported adverse events following atorvastatin and 53% of subjects following placebo. The most frequent adverse event reported following atorvastatin regardless of dose was headache (25%), that occurred more often following placebo (46%) than following atorvastatin.

Adverse events in clinical studies

Introduction

In general, the adverse event rate (excluding laboratory adverse events, to be covered in the next section) and profile of atorvastatin was similar to that of the other HMGRIs, and, at least in the placebo-controlled studies data subset (where mean exposure to active drug and placebo were matched within studies), also similar to placebo. There were no effects of age, gender, or race (to the limits of the data in non-whites) on number or type of AE in atorvastatin-treated patients. Finally, the most common adverse experiences with atorvastatin were GI in nature, all on the order of 2-3% , and not evidently dose-related. This section will briefly summarize some of the analyses presented by the sponsor in the integrated safety summary that serve to illustrate these points.

Adverse events recorded in investigator's terms were converted to preferred terms and body systems using Version IV of the COSTART dictionary.

Adverse events were captured throughout the studies and up to 15 days after stopping treatment. Those that began during active treatment or increased in intensity or frequency from screening or from the placebo-baseline phase were considered treatment emergent.

The investigator determined the intensity of adverse events (mild, moderate, or severe) and their relationship to study medication (definitely not, unlikely, possibly, probably, or definitely related

to study medication, or insufficient information). Treatment-associated adverse events (associated adverse events) were those the investigator considered definitely, probably, or possibly related to treatment or for which there was insufficient information to make a judgement, or those for which no relationship was designated on the CRF. Investigators were instructed to report as serious those adverse events that met FDA criteria of serious: those that were cancer; resulted in death; were life-threatening, permanently disabling, or a congenital anomaly; required or prolonged hospitalization; or were an overdose (accidental or intentional).

No objective criteria were established for reporting laboratory deviations as adverse events. Thus, reporting of laboratory abnormalities as adverse events was inconsistent within and across studies. Because of this fact, lab abnormalities, with particular emphasis on liver function tests and CPK, will be discussed in a separate section.

All and associated adverse events
The incidence of adverse events in patients treated with atorvastatin versus placebo and comparator agents will be examined in several of the data subsets.

Placebo-controlled data set
In the placebo-controlled data subset, direct comparison can be made between the atorvastatin and placebo-treated patients within a patient subset in which mean exposures in the two groups within the individual studies were fairly well matched, and where dose-related adverse events might be detected.

Of 1122 atorvastatin-treated patients, 61% had 1 or more adverse event as compared to 59% of 270 placebo-treated patients. About 14% of both groups had 1 or more associated adverse events. There was no consistent dose-related trend in the percentage of patients with all or associated adverse events. The 10 mg atorvastatin group had the highest overall incidence of adverse events (~64%) but had a lower associated adverse event rate than placebo. The 80 mg group had the highest associated adverse event rate (~18%) and there was a trend toward increasing rates from the 20 to the 40 to the 80 mg dose groups. When the data were normalized for patient-years of exposure, no dose-related effect was evident.

The spectrum of all and associated adverse events experienced by $\geq$1% of patients in the combined atorvastatin dose groups was analyzed relative to placebo and for any dose-related effects. Overall, the adverse event experience was similar between placebo and atorvastatin groups and across doses. There were only two types of events overall that were experienced by at least 1% of patients in the combined atorvastatin groups and that occurred in at least a 3-fold higher rate in that group as compared to placebo. These were abdominal pain (3%) and diarrhea (3%). The incidence of diarrhea did appear to increase with increasing atorvastatin dose, excluding the 20 mg dose group (N=36), up to 5% in the 80 mg group. The placebo group rate was 1%.

As to associated adverse events, 7 types of events occurred at a higher rate among the atorvastatin- than the placebo-treated patients within at least one atorvastatin dose group. These were mostly GI in nature: flatulence, constipation, diarrhea, dyspepsia, nausea, myalgia, and breast pain. There were no dose-related trends for any associated adverse events among the atorvastatin groups. The differences in rates between atorvastatin and placebo groups were on the order of 1 to 2 percent, with absolute rates generally between 0 and 2 or 3 percent. Two patients out of 36 (6%) in the 20 mg dose group did have associated myalgia. The confidence interval around this number as a point estimate of the true incidence of this adverse event is

likely very wide as a function of the small number of patients in this group. All except one instance of breast pain occurred in patients taking atorvastatin plus estradiol.

In short, for all and associated adverse clinical events in this dataset, atorvastatin appeared essentially as well-tolerated as placebo and overall, there were no serious or incremental problems associated with the higher doses of the active drug. The spectrum of adverse events observed, which includes GI and musculoskeletal complaints, is consistent with the other members of this class of drugs.

Fixed dose dataset
The rates for all and associated adverse events were similar in this dataset to those in the placebo-controlled dataset. Again, for associated events, there was a trend toward increasing incidence up to 80 mg atorvastatin, where the rate was ~21%. The spectrum of adverse events was not different than that seen in the previous dataset with the incidence of diarrhea in the atorvastatin-treated patients exceeding that in the placebo group and showing a dose-related trend up to 23 out of 345 (7%) experiencing this event in the 80 mg group. The overall rate in the combined atorvastatin groups (1%) was similar to those seen in the niacin (1.8%) and combined HMGRIs (0.7%) groups, though the absolute numbers were much smaller in the latter two.

One-year studies dataset
In this dataset, the comparison to other HMGRIs and to comparator agents used in the clinical trials is possible. Overall, the incidence of all and associated adverse events was similar for the atorvastatin and combined HMGRI groups. Taken individually, the rates of associated adverse events for each of the marketed HMGRIs were similar to that of atorvastatin and all around 20%. For specific associated adverse events, again the spectrum of types was similar for the marketed HMGRIs and atorvastatin. Again, GI and musculoskeletal symptoms predominated. The rates of these complaints were similar for the atorvastatin and individual marketed HMGRIs, between 1 and 2% for GI complaints. Myalgia occurred in 2% of atorvastatin patients and in 1% of the combined HMGRIs patients.

Within this dataset, there were no effects of age, gender, or race on the incidence of all or associated adverse events among the atorvastatin-treated patients.

All-completed studies data grouping
It is important at the start to point out that this dataset is most useful in the comparison of the active treatments studied. The data for only 110 of the total 270 placebo patients in the NDA database are included in this grouping, for the reason that patients who crossed over from placebo to active therapy were counted as active treatment patients.

Overall, 72% of 2502 atorvastatin-treated patients and 73% of 742 patients treated in the combined HMGRI groups had 1 or more adverse events. The rate of associated events was 20% in the atorvastatin group, 24% in the combined HMGRI group. The types of events were similar to those discussed in reference to the other datasets and are summarized in the table below.

TABLE 8.3.1. All Completed Studies Data Grouping: Associated Adverse Events Experienced by ≥1% of Atorvastatin-Treated Patients

Adverse Event	Placebo N = 110		Atorvastatin N = 2502		Combined HMGRIs N = 742		Colestipol N = 44		Fenofibrate N = 52		Niacin N = 53		Estradiol N = 19	
Constipation	2	(2)	73	(3)	39	(5)	15	(34)	4	(8)	2	(4)	0	(0)
Flatulence	0	(0)	58	(2)	24	(3)	5	(11)	3	(6)	2	(4)	2	(11)
Dyspepsia	0	(0)	56	(2)	14	(2)	2	(5)	3	(6)	1	(2)	1	(5)
Abdominal pain	0	(0)	41	(2)	13	(2)	2	(5)	1	(2)	2	(4)	0	(0)
Headache	2	(2)	37	(1)	14	(2)	1	(2)	2	(4)	5	(9)	1	(5)
Nausea	0	(0)	35	(1)	9	(1)	3	(7)	0	(0)	5	(9)	1	(5)
Myalgia	0	(0)	34	(1)	12	(2)	0	(0)	3	(6)	1	(2)	2	(11)
Asthenia	1	(1)	28	(1)	7	(1)	0	(0)	2	(4)	0	(0)	0	(0)
Diarrhea	0	(0)	27	(1)	11	(1)	1	(2)	2	(4)	4	(8)	1	(5)
Insomnia	0	(0)	26	(1)	9	(1)	0	(0)	0	(0)	1	(2)	0	(0)
Pain	0	(0)	25	(1)	7	(1)	1	(2)	0	(0)	2	(4)	1	(5)
Rash	0	(0)	19	(1)	2	(<1)	2	(5)	2	(4)	8	(15)	0	(0)
Liver Function Tests Abnormal	0	(0)	17	(1)	2	(<1)	0	(0)	1	(2)	0	(0)	0	(0)
Pruritus	0	(0)	14	(1)	4	(1)	0	(0)	0	(0)	4	(8)	0	(0)
Dizziness	0	(0)	14	(1)	7	(1)	0	(0)	0	(0)	4	(8)	1	(5)
ANY EVENT	9	(8)	508	(20)	179	(24)	23	(52)	20	(38)	35	(66)	9	(47)

With regard to overall tolerability of the drug, it is worth pointing out by way of comparison, that atorvastatin showed a lower incidence of all and associated adverse events than colestipol, fenofibrate, niacin, and estradiol. Again, the principal symptomatic complaints with all these agents were GI in origin, though niacin treated patients had a higher incidence of, among other things, dizziness and pruritis and estradiol-treated patients had a higher incidence of breast pain, myalgia, arthralgia than atorvastatin-treated patients, the symptoms in the latter group likely a function of the post-menopausal state of the patients treated with estradiol.

8.4 Adverse events reported with other HMGRIs

The placebo-controlled and all-completed studies dataset were probed for those events commonly associated with this class of drugs.

Myalgia and muscle pain

Myalgia and muscle pain effects were captured in both datasets by combining the following adverse event (COSTART) terms: myalgia, arthralgia, leg cramps, arthritis, bursitis, CPK increased, arthrosis, muscle atrophy, myositis, myasthenia, joint disorder, pain, neck pain, back pain, neck rigidity, chest pain, chest pain substernal, pelvic pain, and bone pain. The proportion of patients with events related to myalgia among atorvastatin- and other HMGRI-treated patients was similar (see table below). No dose-related effect was evident for this constellation of complaints.

TABLE 8.4.1. All Completed Studies Data Grouping: Combined Myalgia and Pain Adverse Events[a]

	Placebo N = 110	Atorvastatin N = 2502	Combined HMGRIs N = 742
AEs, N (%)	14 (13)	533 (21)	173 (23)
Patient-years	29	1845	601
Rate[b]	0.48	0.29	0.29

AE = Adverse event.

[a] Myalgia and muscle pain effects: myalgia, arthralgia, leg cramps, arthritis, bursitis, CPK increased, arthrosis, muscle atrophy, myositis, myasthenia and joint disorder, pain, neck pain, back pain, neck rigidity, chest pain, chest pain substernal, pelvic pain, and bone pain

[b] Number of patients with event + patient-years on treatment

Though there were no confirmed cases of frank myopathy as defined by CK>10X ULN on two consecutive measurements one week apart with accompanying symptoms, there were numerous instances of CK elevated to less than 10X ULN and 3 cases in which a single CK elevation >10X ULN was associated with myalgia. The adverse condition in two of three of those patients were felt due to drug. The muscle effects of atorvastatin will be addressed further in the discussion of changes in CPK levels with treatment.

Rash/allergic reaction

Using the following COSTART terms to capture all allergic reaction, the two datasets were probed for this type of adverse reaction: allergic reaction, photosensitivity reaction, rash, maculopapular rash, face edema, pruritus, pustular rash, skin ulcer, urticaria, exfoliative dermatitis, skin disorder, vesiculobullous rash, eosinophilia, edema, and face edema. The incidence of such reactions was similar in placebo, atorvastatin, and HMGRI treatment groups.

CNS effects

The following COSTART terms were used to probe the dataset for adverse CNS effects: insomnia, asthenia, malaise, depression, anxiety, somnolence, nervousness, amnesia, abnormal dreams, sleep disorder, libido decreased, libido increased, emotional lability, thinking abnormal, apathy, neuropathy, incoordination, peripheral neuritis, twitching, reflexes decreased, and confusion.

There were no marked differences in the rates of such events across atorvastatin, placebo, and combined HMGRI groups.

Cataracts

In the all-completed studies dataset, there were eight instances of cataracts. Five of these occurred in atorvastatin-treated patients, one of whom never received drug. All five had either a history of cataracts or diabetes mellitus. One patient on colestipol, one patient each on lovastatin and pravastatin were noted to have cataracts. Overall, the was no evidence that atorvastatin therapy was associated with an increased risk of cataract formation.

In addition, in one study, 981-08, lenticular opacities were carefully monitored in virtually all patients. This was a 52-week, double-blind, dose-titration study, comparing the safety and efficacy of atorvastatin 10 or 20 mg to that of lovastatin 20 or 40 mg.

In this study, the lens of each eye was assessed by a slit-lamp examination and best corrected visual acuity (Snellen's chart) was determined at baseline and after 52 weeks of treatment. Lens opacities were recorded with a standardized grading system of severity. Slit-lamp examination and visual acuity was determined for 691 to 696 atorvastatin-treated patients and 233 to 235 lovastatin-treated patients.

In short, results indicate no significant clinical or statistical difference in lens opacities and no significant clinical difference in best corrected visual acuity for atorvastatin compared with lovastatin after 52 weeks of treatment.

Summary and conclusions regarding adverse events

The rate and type of all and associated adverse events (excluding laboratory adverse events) in atorvastatin-treated patients are similar to those observed in combined HMGRI groups. No novel adverse events or amplification of reported HMGRI-related adverse events were observed, including myopathy, cataracts, CNS effects, and rash/allergic reactions. With regard to symptomatic measures, atorvastatin was as well or better tolerated than niacin, fenofibrate, colestipol, and estradiol. In short, the adverse event profile of atorvastatin in this NDA database contains no surprises.

8.5 Withdrawals, serious, non-fatal adverse events, and deaths

Withdrawals from clinical studies

Table 8.5.1. All Completed Studies Data Grouping: Withdrawals

	Placebo N = 110		Atorvastatin N = 2502		Combined HMGRIs N = 742		Colestipol N = 44		Fenofibrate N = 52		Niacin N = 53		Estradiol N = 19	
Completed	103	(94)	2276	(91)	665	(90)	41	(93)	40	(77)	43	(81)	15	(79)
Other/ Administrative	4	(4)	112	(4)	40	(5)	0	(0)	2	(4)	2	(4)	1	(5)
Adverse Event	3	(3)	103	(4)	35	(5)	3	(7)	8	(15)	8	(15)	3	(16)

PBO = Placebo.

The table above summarizes the withdrawals from atorvastatin clinical studies, tallied from the all-completed studies data grouping. The data speak not only to the relative tolerabilities of the drugs studied, but also by the high rates of completers, to the quality of both the efficacy and safety data with respect to intent-to-treat for those patients in the placebo, atorvastatin, and combined HMGRI groups, the treatments of most relevance in the review of this NDA. Of the 4% withdrawals due to adverse events in the atorvastatin groups in these studies, half (2%) were felt to be events associated with treatment.

Causes of withdrawals

Events that most often led to withdrawal for atorvastatin-treated patients were related to the digestive system (~1% of patients), body as a whole (~1%), the nervous system (~1%), and the musculoskeletal system (~0.5%). This pattern was also seen for patients treated with other HMGRIs.

Among atorvastatin-treated patients, the incidence of withdrawal for any specific type of adverse event was low, 0.04% to 0.3%. Specific adverse events that most often (at least 5 patients, ≥0.2%) led to withdrawal among atorvastatin-treated patients were abnormal liver function tests (7 patients, 0.3%), nausea (7), abdominal pain (7), pain (6), depression (5), and myalgia (7). These events were considered treatment associated for the majority of patients, with the exception of depression; only 1 of the 5 withdrawals due to depression was considered related to treatment. Review of the medical narratives for withdrawn atorvastatin-treated patients raised no issues challenging the sponsor's conclusion in this regard.

By way of comparison, specific adverse events that most often led to withdrawal among patients who received other HMGRIs were: dyspepsia, headache, and myalgia (3 patients each event, 0.4%). Vomiting was the most frequent adverse event that led to withdrawal for colestipol-treated patients (5%), asthenia for fenofibrate-treated patients (4%), headache and rash for niacin-treated patients (4%), and pain for estradiol-treated patients (11%).

Finally, there was no dose-response in terms of the withdrawal rate in patients on atorvastatin in the clinical database. The table below summarizes the findings by dose.

Table 8.5.2. All Completed Studies Data Grouping: Withdrawal Rate Per Person-Year Due to Adverse Events by Time and Dose

Atorvastatin Dose (mg)	Number of Withdrawals[a]	N	Person-Years	Withdrawal Rate	% Withdrawal
10	64	1677	1083	0.06	0.04
20	14	753	301	0.05	0.02
40	10	493	157	0.06	0.02
80	14	383	222	0.06	0.04

[a] Does not include 1 patient who withdrew receiving 2.5 mg atorvastatin.

Non-fatal, serious adverse events
Investigators were instructed to report as serious any adverse events that met FDA criteria of serious: those that were cancer, resulted in death, were life-threatening, were permanently disabling, were a congenital anomaly, required or prolonged hospitalization, or were an overdose (accidental or intentional).

Of the 2502 atorvastatin-treated patients, 123 (5%) had treatment emergent serious adverse events; 2 of the 2502 patients (<1%) had a serious adverse event associated with treatment. In comparison, 7% of 742 patients treated with other HMGRIs, 2% of 44 colestipol-, and 6% of 52 fenofibrate-treated patients had serious adverse events, none of which were considered treatment related. No niacin- or estradiol-treated patients had serious adverse events.

For atorvastatin-treated patients, serious adverse events were primarily related to the cardiovascular system and body as a whole, with angina pectoris (17/2502 patients), myocardial infarction (7/2502), accidental injury (9/2502), and chest pain (9/2502) the most frequent types of events within each of these body systems. None of these more frequent serious adverse events were considered associated with atorvastatin treatment. Serious adverse events related to the cardiovascular system were expected in this population of patients at risk for cardiovascular disease.

Associated serious adverse events
As stated above, there were two patients who had associated serious adverse events. Their histories are summarized below. Neither event was unequivocally attributable to atorvastatin therapy.

The first patient was a 62 year old man who presented with pancreatitis on day 210 of therapy with atorvastatin 10 mg/day, probably related to the passage of gallstones. The patient recovered (?off medication) and the episode was judged possibly related to study medication.

The second patient was a 51 year old man with a history of diabetes and icterus who presented with icterus, markedly elevated transaminases, and hyperbilirubinemia on day 251 of therapy with atorvastatin 10 mg. The patient had, 4 days prior to this presentation, completed a 16 day course of treatment with paracetamol and acetylcysteine for a viral illness. The patient recovered and transaminases and bilirubin reverted to near normal within 1 week of stopping atorvastatin treatment. Appropriated tests for viral hepatitides revealed only a positive EBV-RIA, suggestive of a previous infection. He was not rechallenged. The episode was considered possibly related to study medication.

In sum, the incidence of serious adverse events associated with this drug were rare, and of the two possibly related to treatment, one was consistent with adverse events seen with other agents of this class.

8.6 Carcinomas

Carcinomas were rare in this clinical database. A total of 10 atorvastatin-treated patients with a definitive diagnosis of carcinoma were noted in the All Completed Studies data grouping (10/2502 = 0.4%). One carcinoma was identified in a lovastatin-treated patient (1/260 = 0.4%). In six of the 10 atorvastatin-treated patients the carcinoma was noted within 4 months of the initiation of study medication, and 5 of these 6 patients had a past medical history that indicated signs or symptoms associated with the development of cancer. The remaining 4 patients were diagnosed with cancer at various times from Study Day 134 through 350. Since a thorough examination specifically for detecting possible cancer was not performed on patients before they entered atorvastatin clinical studies, the relationship of these cancers to treatment with study medication cannot be determined. However, there were numerous cell types reported and several cancers that were at an advanced stage or were in patients with a past history of cancer. In addition, many of the cancers are known to be slow growing. Thus, it is unlikely that these cancers were related to study medication or to cholesterol reduction.

Consistent with the evaluation of carcinomas in the All Completed Studies data grouping, the number of carcinomas in ongoing studies were identified. Eight (8/2313 = 0.3%) atorvastatin-treated patients, 3 (3/401 = 0.7%) lovastatin-treated patients, 2 (2/225 = 0.9%) fluvastatin-treated patients, and 5 (5/992 = 0.5%) patients in the combined HMGRI group (lovastatin, pravastatin, simvastatin, and fluvastatin) were diagnosed with carcinomas in various organ systems and of various cell types. In addition, skin carcinoma (basal cell or squamous) and benign tumors (COSTART = Neoplasm) were diagnosed in all treatment groups. One atorvastatin-treated patient, Patient 028, Study 981-062, Center 014, reported hematuria in completed Study 981-008, Center 014, which was diagnosed as bladder cancer after the patient entered ongoing Study 981-062.

In sum, when the completed and ongoing studies are considered together, the incidence of cancer in the atorvastatin group was similar to that in the combined HMGRI groups. Overall, there is no good evidence in this NDA that treatment with atorvastatin or cholesterol reduction *per se* can be predicted to be associated with an increased incidence or diagnosis of cancer. This is quite consistent with the data from long-term clinical trials using members of this class, with one exception: In the recently completed and published CARE study using pravastatin, there was an as yet unexplained excess of breast cancer cases among women in the active treatment group.

Table 8.6.1. Carcinomas

Drug	Dose (mg)	Day of Onset	Tumor Type	Costart Term	Outcome	Age	Sex	Relevant History
Atorvastatin	10	250	metastatic lung carcinoma - (R) and (L) lobe	Carcinoma of lung	Death-pulmonary embolism CA - discovered on autopsy	54	M	N/A
Lovastatin	20	106	Prostate Cancer	Prostatic Carcinoma	Recovered	59	M	N/A
Atorvastatin	10	106	Chronic lymphocytic leukemia	Chronic lymphocytic leukemia	Not yet recovered	58	M	Elevated WBC and lymphocytes at screening
Atorvastatin	10	328	Adenocarcinoma of prostate	Prostatic Carcinoma	Not yet recovered	59	M	
Atorvastatin	10	36	Chronic lymphocytic leukemia	Chronic lymphocytic leukemia	Not yet recovered	58	F	Mild lymphocytosis
Atorvastatin	10	120	ovarian adenocarcinoma	Carcinoma	Death	67	F	Hysterectomy
Atorvastatin	10	70	Hypernephroma of (R) kidney	Neoplasm	Not yet recovered	80	M	N/A
Atorvastatin	20	134	Grade III ductal carcinoma of the breast	Breast Carcinoma	Not yet recovered	61	F	N/A
Atorvastatin	10	38	Melanoma (lentigo maligna)	Skin melanoma	Recovered	68	F	Hutchinson's Melanotic freckle
Atorvastatin	20	51	Infiltrating Ductal Carcinoma	Breast Cancer	Recovered	70	F	(L) benign breast disease
Atorvastatin	20	350	cancerous mass in fallopian tubes	Carcinoma	Not yet recovered	63	F	N/A

8.7 Deaths

Total atorvastatin exposure in the 21 completed studies was 1845 patient-years. A total of 11 patients, 6 men and 5 women, died from events considered unrelated to study medication; 9 (0.4%) of 2502 atorvastatin-treated patients, 1 (0.6%) of 172 pravastatin-treated patients, and 1 (1.9%) of 52 fenofibrate-treated patients (Table). Medical narratives for the atorvastatin-treated patients who died were reviewed. Two of the 9 atorvastatin patients who died did so due to cancer from 3 to 5 months after discontinuing atorvastatin treatment. Causes of death for the remaining patients were primarily cardiovascular-related events. Cardiac deaths, myocardial infarction and sudden death were not related to time on drug and occurred in patients who had a history of heart disease. Thus, these events were not unexpected.

TABLE 8.7.1. All Completed Studies Data Grouping: Listing of Patients Who Died

Study 981-	Center	Patient	Age/Gender	Adverse Event COSTART/ Investigator's Term	Treatment/ Last Known Dose (mg/day)	Study Day AE Began	Day of Death	Relationship to Drug	Narrative Number
Patients Receiving Atorvastatin at Time of Death									
008	003	034	55/M	PULMONARY EMBOLISM	Atorva/10	250	250	Unlikely	D.1
				CARCINOMA OF LUNG/ Lung Cancer w/Bone & Lymph Node Metastases	Atorva/10	250	250	Unlikely	
008	010	006	68/W	SUBARACHNOID HEMORRHAGE	Atorva/10	41	51	Unlikely	D.2
008	016	018	59/M	SUDDEN DEATH	Atorva/10	130	130	Unlikely	D.4
009	014	001	67/W	OVARIAN CARCINOMA	Atorva/10	118	393	Definitely Not	D.5
056	002	105	65/M	MYOCARDIAL INFARCTION	Atorva/80	122	122	Definitely Not	D.6
056	017	213	72/W	SUDDEN DEATH	Atorva/40	259	259	Unlikely	D.7
057	003	026	74/W	DEATH/Death[a]	Atorva/80	313	313	Unlikely	D.8
Patients Who Had Discontinued Atorvastatin >3 Months Before Death									
008	010	011	68/W	CARCINOMA/ Pelvic Mass Ovarian Cancer	Atorva/10	294	566	Definitely Not	D.3
057	014	011	54/M	DEATH/--[b]	Atorva/None[b]	395[c]	395[c]	Unlikely	D.9
Patients on Medications Other Than Atorvastatin									
009	009	027	65/M	CEREBROVASCULAR ACCIDENT	Prava/20	224	225	Unlikely	--
055	007	111	52/M	MYOCARDIAL INFARCTION	Fenofibrate/300	46	46	Unlikely	--

AE = Adverse Event; Atorva = Atorvastatin; Prava = Pravastatin; -- = no narrative provided.
[a] Patient died due to heart insufficiency.
[b] Patient died due to cancer 5 months after discontinuing atorvastatin because of lack of compliance.
[c] Approximate study day

As of March 15, 1996, a total of 4 patients have died in ongoing studies due to events not considered related to treatment. Three of these patients (0.1% of 2313 patients) had received atorvastatin.

TABLE 8.7.2. Listing of Patients Who Died in Ongoing Studies

Study 981-	Center	Patient	Age/Gender	Adverse Event COSTART/ Investigator's Term	Treatment/ Last Known Dose (mg/day)	Study Day AE Began	Day of Death	Relationship to Drug	Narrative Number
Atorvastatin									
026	032	001	52/M	Sudden Cardiac Death	20	327	327	Definitely not	D.227
062	008	029	70/M	Pulmonary Edema	20	28	28	Unlikely	D.228
069	007	009	53/M	Myocardial Infarction	10	17	18	Unlikely	D.229
Simvastatin									
069	006	012	76/M	Motor Vehicle Accident	Simvastatin 10	79	95	Definitely not	--

AE = Adverse Event

8.8 Changes in clinical laboratories

The normal range for laboratory parameters was determined by the designated laboratory for each study. Of the 21 completed studies, 17 were multicenter trials that used 1 of 6 central, certified laboratories; the remaining 4 studies were single-center and used local laboratory facilities.

In order to "scan" the database for adverse laboratory consequences of atorvastatin therapy, the sponsor has presented analyses of median changes from baseline to end of study in laboratory parameters as well as of incidence of abnormal lab values. The results of these "scanning" analyses will be followed by analyses and discussion of specific laboratory abnormalities associated with atorvastatin therapy.

Median changes from baseline to the end of study

Median changes from baseline to the end of the study for the 21 completed studies were determined for patients with at least 1 baseline measurement and 1 measurement during treatment. Results are reviewed for the Placebo-controlled and All-completed studies datasets. Results were qualitatively similar in all four datasets.

Placebo-controlled data grouping

Shown in the table below, ALT, AST, and Alk Phos were the only parameters whose median change from baseline increased consistently with increasing atorvastatin dose. However, but for the value in the 40 mg group, median change from baseline in CPK, too, appears to increase with increasing drug dose. Not shown in the table are non-dose-dependent decreases in platelet counts ranging from -2500 to -10,000 per cubic millimeter. The changes in liver enzymes and CPK are known effects of the statins. The changes in platelet counts are inconsistent and not clinically significant.

Table 8.8.1. Placebo-controlled data grouping: Dose-related changes in clinical laboratories

	Placebo	N=270	Ator 10	N=863	Ator 20	N=36	Ator 40	N=79	Ator 80	N=94	All Ator	N=1110
	Median change	N	Median change	N	Median change	N	Median change	N	Median change	N	Median change	N
Variable (Units)												
ALT (U/L)	0	267	2	855	3.5	36	5	78	10	91	2	1110
AST (U/L)	0	267	0	855	1.5	36	2	78	5	91	1	1110
Alk Phos (U/L)	0	262	1	838	1.5	36	4	78	7	91	1	1093
CPK (U/L)	1	267	2	855	4.5	36	3	78	9	91	2	1110

The table below shows the median changes from baseline to the end of study in the atorvastatin group that were different from placebo. These data corroborate the findings in the placebo-controlled dataset with the addition of the glucose elevations. Similar changes occurred in the combined HMGRIs group, though to a lesser degree in all cases, save for the changes in platelet counts.

Table 8.8.2. All-completed studies: Median changes from baseline in clinical laboratories

	Placebo	N=110	Atorvastatin	N=2502	Combined HMGRIs	N=736
	Median change	N	Median change	N	Median change	N
Variable (units)						
ALT (U/L)	0	108	3	2483	1	735
AST (U/L)	0	108	1	2483	1	735
Alk Phos (U/L)	0	108	3	2471	0	731
CPK (U/L)	1.5	108	5	2421	3	735
Glucose (mg/dl)	0	106	2	2427	1.4	682
Platelets ($x10^3/mm^3$)	3.5	102	-8	2441	-8	674

Incidence of clinical laboratory abnormalities

The table below summarizes the clinical lab abnormalities, as defined by criteria for clinically meaningful changes, in the placebo-controlled data grouping. Most striking was the incidence of ALT and AST elevations to greater than the upper limit of normal (ULN) that appeared to be dose-related, with 45% of the 80 mg treatment group having at least one ALT value >ULN and 39% having an AST value >ULN.. AST abnormalities paralleled ALT elevations throughout the database. Also of interest is the increased incidence of CPK and glucose elevations in the atorvastatin group.

Table 8.8.3. Placebo-Controlled Data Grouping: Clinical Laboratory Abnormalities [Number (%) of Patients]

Laboratory Parameter	Criteria	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94	Combined[a] Atorvastatin N = 1122
Alk Phos	>3.00 × ULN	1 (<1)	0 (0)	0 (0)	0 (0)	3 (3)	3 (<1)
ALT	>ULN	31 (11)	139 (16)	4 (11)	27 (34)	42 (45)	219 (20)
AST	>ULN	25 (9)	110 (13)	4 (11)	19 (24)	37 (39)	176 (16)
BUN	>2.00 × ULN	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
CPK	>5.00 × ULN	0 (0)	4 (<1)	0 (0)	1 (1)	1 (1)	6 (1)
Glucose	>1.25 × ULN	3 (1)	30 (3)	2 (6)	1 (1)	4 (4)	37 (3)
Hematocrit	<0.75 × LLN	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Hemoglobin	<0.75 × LLN	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Total Bilirubin	>1.50 × ULN	1 (<1)	9 (1)	0 (0)	1 (1)	2 (2)	15 (1)
WBC	<0.75 × LLN	4 (1)	9 (1)	0 (0)	2 (3)	1 (1)	12 (1)
	>1.50 × ULN	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)
Any Abnormality		44 (16)	214 (25)	8 (22)	33 (42)	50 (53)	314 (28)

Alk Phos = Alkaline Phosphatase; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; BUN = Blood Urea Nitrogen; CPK = Creatine Phosphokinase.

[a] Contains data for patients who received 2.5 mg (N = 11), 5 mg (N = 26), and 60 mg (N = 13) atorvastatin.

In the **all-completed studies** data grouping, the incidence of lab abnormalities in the combined atorvastatin group was compared to the placebo and to the combined HMGRIs groups. 683/2502 (27%) of atorvastatin patients as compared to 147/742 (20%) and 18/110 (16%) of the combined HMGRIs and placebo groups, respectively, had at least one ALT level >ULN. 1% of both atorvastatin and HMGRI groups had CPK> 5X ULN. Glucose elevation >1.25 X ULN occurred

in 7% of atorvastatin patients, in 11% of the combined HMGRIs group, and in 1% of the placebo patients.

Specific laboratory abnormalities

Plasma glucose elevations
The increased incidence of glucose elevations in the atorvastatin-treated patients bears comment. In the placebo-controlled data grouping, of the 37 atorvastatin patients with glucose elevations, 36/37 had elevated glucose at baseline, and in 25 of those 36, elevations were >1.25 X ULN. In addition, 7/37 had a history of diabetes and 2/37 had a history of glucose intolerance.

Similarly, in the all-completed studies grouping, of 185 atorvastatin patients with glucose elevations, 115/185 had a history of NIDDM. 174/185 had baseline values > ULN.

In sum, there is little evidence for an effect of atorvastatin on glucose metabolism.

Elevations in ALT and AST
Of these 2 enzymes, ALT was the most consistent indicator of atorvastatin's effect on liver function. No patient had a clinically important elevation in AST independent of ALT. Thus, the discussion will be restricted to ALT elevations.

Mean ALT levels over time
An analysis of mean ALT levels at each dose of atorvastatin by week on study up to 16 weeks in the placebo-controlled trials (981-04, 10, 25, 96, 08) was performed. There was little effect of increasing time on drug for the lower doses. Over time, however, the mean ALT level in those patients taking 80 mg does increase. At weeks 4 to 16, ALT values for the 80 mg group are statistically significantly higher than those for the placebo group ($p<.005$) though the absolute differences in the means are small (placebo mean ~15 U/L, 80 mg atorvastatin ~30 U/L). This is consistent with the dose-related effect in incidence of ALT >ULN shown above, but also may suggest a cumulative dose effect, at least at this high dose.

Maximal elevations in ALT
As shown in table 8.8.3 above, the incidence of ALT elevations to >ULN among atorvastatin-treated patients was dose-dependent in this database. An analysis of maximal elevations allows us to examine the distribution of abnormal ALT levels by degree across the study population and to examine the relationship to dose and to compare the effect of atorvastatin, placebo, and combined HMGRIs in this regard.

The table below shows that in the **fixed-dose grouping**, there appears to be, at least in the subgroup with ALT <1 x ULN at baseline, a dose-related increase in the percentage of patients having a maximal level higher than baseline. Furthermore, on the basis of the percentage of patients overall (see "All Values") having maximal ALT within normal, the combined HMGRIs appear as well tolerated as the 10 or 20 mg atorvastatin dose and significantly better so than the 40 and 80 mg doses. Finally, when the atorvastatin patients are considered irrespective of starting ALT, there appears to be a dose-related increase in the percentage of patients having maximum ALT levels in each of the three intervals above normal listed in the table. This analysis is consistent with the increase in median changes in ALT from baseline seen with increasing dose of atorvastatin presented earlier.

Table 8.8.4. Fixed-Dose Data Grouping: Maximum ALT Levels By Baseline ALT Level [Number (%) of Patients]

Baseline ALT Value/ Treatment/Dose at Screening	Number[a] of Patients	Treatment Phase							
		≤1 × ULN		>1-≤2 × ULN		>2-≤3 × ULN		>3 × ULN	
≤1 × ULN									
Placebo	233	214	(92)	16	(7)	1	(0)	2	(1)
Atorvastatin (combined doses)	2052	1762	(86)	252	(12)	22	(1)	16	(1)
10.0 mg	1442	1310	(91)	125	(9)	7	(0)	0	(0)
20.0 mg	169	149	(88)	17	(10)	3	(2)	0	(0)
40.0 mg	71	50	(70)	17	(24)	2	(3)	2	(3)
80.0 mg	302	191	(63)	88	(29)	9	(3)	14	(5)
Combined HMGRIs	501	467	(93)	33	(7)	0	(0)	1	(0)
>1 × ULN									
Placebo	34	11	(32)	21	(62)	1	(3)	1	(3)
Atorvastatin (combined doses)	202	67	(33)	108	(54)	21	(10)	6	(3)
10.0 mg	134	48	(36)	71	(53)	12	(9)	3	(2)
20.0 mg	17	9	(53)	8	(47)	0	(0)	0	(0)
40.0 mg	7	1	(14)	5	(71)	0	(0)	1	(14)
80.0 mg	39	7	(18)	21	(54)	9	(23)	2	(5)
Combined HMGRIs	34	16	(47)	17	(50)	1	(3)	0	(0)
All Values									
Placebo	267	225	(84)	37	(14)	2	(1)	3	(1)
Atorvastatin (combined doses)	2254	1829	(81)	360	(16)	43	(2)	22	(1)
10.0 mg	1576	1358	(86)	196	(12)	19	(1)	3	(0)
20.0 mg	186	158	(85)	25	(13)	3	(2)	0	(0)
40.0 mg	78	51	(65)	22	(28)	2	(3)	3	(4)
80.0 mg	341	198	(58)	109	(32)	18	(5)	16	(5)
Combined HMGRIs	535	483	(90)	50	(9)	1	(0)	1	(0)

[a] Number of patients with both a baseline and posttreatment measurement.

Analysis of maximum ALT levels in the **all-completed studies** grouping (below) reveals that for those patients with normal starting ALT levels, atorvastatin patients tended more frequently than did placebo and combined HMGRI patients to have maximum ALT levels above their starting value. In addition, overall a higher percentage of patients in the placebo (77%) and combined HMGRI (78%) groups had maximal ALT within the normal range throughout the studies than did the atorvastatin-treated patients (71%).

Table 8.8.5. All Completed Studies Data Grouping: Maximum ALT Levels By Baseline ALT Level

Baseline ALT Value/ Treatment	Number[a] of Patients	Treatment Phase							
		≤1 × ULN		>1-≤2 × ULN		>2-≤3 × ULN		>3 × ULN	
≤1 × ULN									
Placebo	85	75	(88)	9	(11)	0	(0)	1	(1)
Atorvastatin (combined doses)	2259	1717	(76)	459	(20)	52	(2)	31	(1)
Combined HMGRIs	675	561	(83)	100	(15)	9	(1)	5	(1)
>1 × ULN									
Placebo	23	8	(35)	14	(61)	1	(4)	0	(0)
Atorvastatin (combined doses)	224	44	(20)	138	(62)	30	(13)	12	(5)
Combined HMGRIs	59	13	(22)	34	(58)	11	(19)	1	(2)
All Values									
Placebo	108	83	(77)	23	(21)	1	(1)	1	(1)
Atorvastatin (combined doses)	2483	1761	(71)	597	(24)	82	(3)	43	(2)
Combined HMGRIs	734	574	(78)	134	(18)	20	(3)	6	(1)

[a] Number of patients with both a baseline and posttreatment measurement.

Clinically important ALT elevations

Clinically important ALT elevations were those that were >3 x ULN on two consecutive measurements 4 to 10 days apart. The distribution of such elevations in atorvastatin treated patients by dose is shown in the table below. This table includes all patients exposed to atorvastatin in clinical trials.

TABLE 8.8.6. Incidence of Clinically Important ALT Elevations by Number of Patients Exposed to Atorvastatin

Dose (mg)	Number of Patients Exposed	Patients With Elevations	Percent of Patients
10	1677	2	0.1
20	753	0	0.0
40	493	4	0.8
80	383	13	3.4

Out of 3522 total patients enrolled in clinical studies in this NDA, 25 (0.7%) had clinically important ALT elevations. Only one patient was symptomatic. The distribution of patients among treatment groups was as follows: 19/2502 (0.7%) in the atorvastatin group, 1/270 (0.4%) in the placebo group, 1/314 (0.3%) in the colestipol group, 3/260 (1%) of the lovastatin group, and 1/52 (1.9%) in the fenofibrate group.

In the atorvastatin groups, the incidence of clinically important ALT elevations was dose related, with a striking rate of occurrence in the 80 mg group. The study day on which these abnormalities were first observed ranged from number 46 to number 365, with 10 of 19 occurring in the first 12 weeks after starting treatment and 9 of these 10 in the interval from 7 to 12 weeks.

The disposition of these 19 patients is telling. Nine of the patients ultimately withdrew because of persistent elevations to >3 x ULN despite dose reduction. ALT returned to pretreatment levels in all 9, most within 3 to 9 weeks. The remaining 10 patients completed their respective studies after reduction in dose. For 8 of the 10 patients who completed their studies, ALT levels had returned to within normal limits at the time of the last follow-up visit, and 6 of the 8 subsequently entered into extension study 981-077. One of these had a clinically important AST elevation during therapy in the extension study. For the other 2 of the 10 patients completing treatment, values had declined to <3 × ULN but were not within normal limits at the end of the double-blind study. Of note, these 2 patients continued with atorvastatin treatment in extension Study 981-077 with, for the most part, consistent minor ALT elevations (<3 x ULN). None of the 19 atorvastatin-treated patients suffered sequelae due to their clinically important ALT elevations.

Reviewer's comments on LFT abnormalities
In summary, overall, the incidence of clinically important LFT abnormalities associated with atorvastatin therapy was low (<1%) in this database. However, it must be remembered that the safety data are weighted toward the 10 mg dose, with >50% of the total exposure at that dose.

Examination of the data reveals that, in the atorvastatin-treated patients, there were dose-related increases in median changes in ALT from baseline, dose-related increases in the incidence of ALT > ULN, dose-related increases in the percentage of patients who had maximal ALT levels greater than baseline, irrespective of starting level. Furthermore, atorvastatin at higher doses was more likely to induce these abnormalities than were the combined HMGRIs studied. Finally, in addition to the dose-related increased incidence of minor LFT abnormalities, there was a striking increased incidence of clinically important ALT elevations in the 80 mg atorvastatin group. The exposure to 20 mg and 40 mg was inadequate (most was in shorter treatment protocols) to assess whether there is a continuous dose-response. Clearly, however, the incidence is higher at 80 mg than at 10 mg.

All that being said, there were no sequelae of any of these ALT elevations, most importantly of the clinically important ones. Clearly, elevations in LFTs are known to occur with the statins, presumably related to the mechanism of action of the drugs, though relatively rare and idiosyncratic in character even while being dose-related. As such, these are adverse events for which patients are regularly monitored. These adverse reactions are expected, labeled (for the other statins), and while potentially clinically significant, in practice, they have not been found to pose serious problems. Furthermore, in the atorvastatin cases and in the data from other statins, the changes are reversible on lowering or discontinuing the drugs. Indeed, it is often possible to treat through minor elevations in LFTs after reduction in dose, as was true in a number of the cases reported here.

Nevertheless, the fact that the higher doses of atorvastatin are clearly more hepatotoxic than the HMGRIs to which they can be compared (lovastatin , pravastatin , simvastatin), suggests that consideration should be given to more frequent monitoring of LFTs early in the treatment course in patients on atorvastatin 40 and 80 mg. Because of the increased incidence of chemical

hepatitis expected at these doses, until sufficient long term experience is obtained, it seems reasonable to attempt to obviate against a relatively high percentage of patients' experiencing prolonged (albeit usually asymptomatic) elevations in hepatic enzymes.

Labeling should communicate the fact that with increasing doses of atorvastatin, higher rates of LFT elevations are expected, both <3 x ULN and >3 x ULN. Furthermore to cite only an overall rate of clinically important ALT elevations of <1% is potentially misleading. At 80 mg, the rate was 3.4% in the completed atorvastatin clinical trials. The disposition of the patients with clinically important ALTs can be summarized to emphasize reversibility and the absence of sequelae. Monitoring should be recommended before initiation of treatment, after 6 to 12 weeks, and again at around 18 weeks, and similarly after dose adjustments. Once on a fixed dose, LFTs should be monitored at least every 6 months thereafter with appropriate measures taken in the event of significant, persistent LFT abnormalities.

CPK elevations

Introduction

Myalgia is a relatively common symptom among patients treated with HMGRIs and was reported by 34/2502 (1.4%) of atorvastatin treated patients studied here. Musculoskeletal complaints were offered by over 20% of both atorvastatin and combined HMGRIs patients. Frank myopathy, which occurs very rarely with this class of drugs, is signaled by the occurrence of muscle pain or tenderness in association with elevated CPK and may lead to rhabdomyolysis, especially in patients with renal insufficiency. The muscle effects of the HMGRIs are presumed to be related to the mechanism of action of the drug, but because of their infrequent occurrence, must be considered idiosyncratic. The risk of myositis, myopathy, and rhabdomyolysis are known to be increased by concomitant use of HMGRIs and certain other agents, including the fibrates, cyclosporine, erythromycin, and itraconazole. The mechanism of this enhanced toxicity is felt due to increase in systemic levels of HMGRI because of inhibition of hepatic drug metabolizing enzymes, specifically cytochrome P450 CYP3A4.

In the atorvastatin development program, CPK levels were monitored in 2-week to 6-month intervals to ensure the patient's safety. A CPK value >10 × ULN at 2 consecutive measurements taken 4 to 10 days apart with muscle pain, tenderness, or weakness was considered clinically important.

No atorvastatin-treated patient in completed or ongoing studies had a clinically important CPK elevation. There were, however, patients with 1 CPK measurement >10 × ULN and concurrent muscle pain, tenderness, or weakness, as well as patients (in ongoing studies) with 2 CPK measurements >10 × ULN without concurrent muscle symptoms. The review of these safety data reveals that, in general, myopathic effects of atorvastatin are rare, as is the case with the other statins, are idiosyncratic in nature, with no apparent dose effect on incidence.

The review of CPK elevations associated with atorvastatin therapy will include first an analysis of maximum levels with respect to the upper limit of normal (ULN), and will include examination of the effect of dose as well as a comparison to the other HMGRIs studied in this clinical database.

Maximum CPK levels

The table below shows that for the fixed-dose data grouping overall, the vast majority of patients treated with in the combined atorvastatin and other HMGRI groups (~98%) had maximum CPK levels <3 x ULN. When the overall data are examined by dose of atorvastatin, there is a trend, at least from the 10 mg to the 80 mg group, in the incidence of maximum levels >3 x ULN. Specifically, 11/341 (3.2%) of patients in the 80 mg group compared to 34/2254 (1.2%) of patients in the atorvastatin 10 mg group had maximum CPK >3 x ULN. In addition, only 9/535 (1.7%) of patients in the combined HMGRI group had similar elevations. The incidence among placebo patients was 0.7%.

TABLE 8.8.7. Fixed-Dose Data Grouping: Maximum CPK Levels by Baseline CPK Level

CPK Values by Treatment Group/Dose at Screening/ Baseline	Number[a] of Patients	FIXED DOSE STUDIES Treatment Phase ≤3 × ULN	3-≤5 × ULN	5-≤10 × ULN	>10 × ULN
≤3 × ULN					
Placebo	267	265 (99)	2 (1)	0 (0)	0 (0)
Atorvastatin (combined)	2223	2195 (99)	22 (1)	4 (0)	2 (0)
10.0 mg	1557	1540 (99)	13 (1)	3 (0)	1 (0)
20.0 mg	184	183 (99)	1 (1)	0 (0)	0 (0)
40.0 mg	75	73 (97)	1 (1)	1 (1)	0 (0)
80.0 mg	334	326 (98)	7 (2)	0 (0)	1 (0)
Combined HMG-CoA	531	522 (98)	6 (1)	3 (1)	0 (0)
>3 × ULN					
Placebo	0	0 (0)	0 (0)	0 (0)	0 (0)
Atorvastatin (combined)	31	25 (81)	2 (6)	3 (10)	1 (3)
10.0 mg	19	16 (84)	1 (5)	2 (11)	0 (0)
20.0 mg	2	2 (100)	0 (0)	0 (0)	0 (0)
40.0 mg	3	3 (100)	0 (0)	0 (0)	0 (0)
60.0 mg	0	0 (0)	0 (0)	0 (0)	0 (0)
80.0 mg	7	4 (57)	1 (14)	1 (14)	1 (14)
Combined HMG-CoA	4	4 (100)	0 (0)	0 (0)	0 (0)
All Values					
Placebo	267	265 (99)	2 (1)	0 (0)	0 (0)
Atorvastatin (combined)	2254	2220 (98)	24 (1)	7 (0)	3 (0)
10.0 mg	1576	1556 (99)	14 (1)	5 (0)	1 (0)
20.0 mg	186	185 (99)	1 (1)	0 (0)	0 (0)
40.0 mg	78	76 (97)	1 (1)	1 (1)	0 (0)
80.0 mg	341	330 (97)	8 (2)	1 (0)	2 (1)
Combined HMG-CoA	535	526 (98)	6 (1)	3 (1)	0 (0)

[a] Number of patients with both or baseline and posttreatment measurement.

In the analysis of the **all-completed studies** dataset, shown in the table below, again the vast majority of patients in placebo, combined atorvastatin, and combined HMGRIs groups had maximum CPK levels <3 x ULN. It is interesting, however, that the only levels >10 x ULN were in atorvastatin patients, with an incidence of 0.4% (11/2483). Three instances occurred in patients with CPK elevated at baseline, but 8 of 11 were in patients with normal baseline CPK. Of the 11 patients, only 3 had concurrent symptoms of muscle pain, tenderness, or weakness. One of the patients was a marathon runner who had recently completed a race. The distribution of these cases by dose of atorvastatin is shown in the second table below. There is no apparent dose-related increase in the incidence of maximum CPK levels for any of the intervals above normal listed in the table. This supports the idiosyncratic nature of the myopathic effects of this class of drugs (short of the known drug-drug interactions).

TABLE 8.8.8. All Completed Studies Data Grouping: Maximum CPK Levels by Baseline CPK Level

CPK Values by Treatment Group/Dose at Screening/ Baseline	Number[a] of Patients	ALL COMPLETED STUDIES Treatment Phase ≤3 × ULN	3-≤5 × ULN	5-≤10 × ULN	>10 × ULN
≤3 × ULN					
Placebo	108	106 (98)	2 (2)	0 (0)	0 (0)
Atorvastatin (combined)	2452	2390 (97)	39 (2)	15 (1)	8 (<1)
Combined HMG-CoA	730	707 (97)	16 (2)	7 (1)	0 (0)
>3 × ULN					
Placebo	0	0 (0)	0 (0)	0 (0)	0 (0)
Atorvastatin (combined)	31	24 (77)	3 (10)	1 (3)	3 (10)
Combined HMG-CoA	4	4 (100)	0 (0)	0 (0)	0 (0)
All Values					
Placebo	108	106 (98)	2 (2)	0 (0)	0 (0)
Atorvastatin (combined)	2483	2414 (97)	42 (2)	16 (1)	11 (0)
Combined HMG-CoA	734	711 (97)	16 (2)	7 (1)	0 (0)

[a] Number of patients with both a baseline and posttreatment measurement.

Table 8.8.9. Summary of maximum CPK levels by dose. All completed studies.

Dose	Number of patients[a]	>3<5 x ULN	>5<10 x ULN	>10 x ULN
0[b]	99	1 (1)	1 (1)	0 (0)
10	1395	20 (1)	6 (<1)	5 (<1)
20	366	6 (2)	3 (1)	2 (1)
40	204	6 (3)	5 (2)	1 (<1)
80	346	9 (3)	1 (<1)	3 (1)

[a] Number of patients is the number of patients whose maximum elevation was at the dose indicated, not the number of patients receiving that dose.
[b] Patient was on 0 dose at time of the event

Ongoing studies

One patient on atorvastatin 10 mg had a CPK level of 23,900 U/L on day 171 of treatment. The patient had previous completed another study and had a total atorvastatin exposure of 535 days. The CPK level fell to 2080 U/L by day 175 and to near normal 10 days later. There were no symptoms.

One lovastatin 80 mg patient had a clinically important CPK elevation first noted on day 85 of therapy and resolved by day 99.

Reviewer's comments on CPK abnormalities

The data reviewed suggest no extraordinary muscle toxicity for atorvastatin relative to the other HMGRIs, based both upon the head-to-head comparison trials as well as on historical data. Furthermore, neither the incidence of all elevations to greater than 3 X ULN nor the incidence of clinically important (persistent, marked, and symptomatic) elevations appears to be dose-related. The muscle effects of atorvastatin appear idiosyncratic in nature, consistent with other members of the class.

8.9 Crystalline atorvastatin

As mentioned earlier, during development, the physical form of atorvastatin changed from amorphous to crystalline as a consequence of optimization of purification and chemical manufacturing. Crystalline atorvastatin is significantly purer, contains no new impurities and is more stable than the amorphous form. No significant changes to the dosage form manufacturing process were necessary when using the crystalline material. The crystalline drug substance will be used to produce atorvastatin tablets intended for commercial distribution.

In pharmacokinetic studies, the rate but not the extent of absorption of crystalline atorvastatin was slightly though significantly increased over the amorphous form.

Exposure to crystalline atorvastatin

In the original NDA submission, the only data on crystalline atorvastatin in a completed study come from study 981-96, the small dose-ranging study discussed in the review of efficacy. All told, 56 patients received atorvastatin for up to 6 weeks in this study, with from 10 to 13 patients receiving 10, 20, 40, 60, or 80 mg/day.

The table below compares the safety profile of amorphous atorvastatin in study 981-04 to that of crystalline atorvastatin in study 981-96. For all and associated adverse events crystalline atorvastatin showed greater rates than the amorphous form, although the placebo group adverse event rate was also greater in study 981-96. The rest of the profiles appear similar.

TABLE 8.9.1. Comparison of Safety Profiles of Patients Treated With Amorphous (Study 981-004) or Crystalline (Study 981-096) Atorvastatin
[Number (%) of Patients]

Events	Study 981-004				Study 981-096			
	Placebo N = 12		Amorphous Atorvastatin N = 69		Placebo N = 9		Crystalline Atorvastatin N = 56	
Overall Adverse Events	4	(33)	30	(43)	5	(56)	35	(63)
Associated Adverse Events	1	(8)	6	(9)	0	(0)	9	(16)
Serious Adverse Events	0	(0)	1	(1)[a]	0	(0)	0	(0)
Deaths	0	(0)	0	(0)	0	(0)	0	(0)
Withdrawals Due to Adverse Events	0	(0)	1	(1)[b]	0	(0)	0	(0)
Clinically Important ALT/AST Elevations[c]	0	(0)	1	(1)	0	(0)	0	(0)
Clinically Important CPK Elevations[d]	0	(0)	0	(0)	0	(0)	0	(0)

[a] Accidental injury
[b] Influenza
[c] Two consecutive values >3 × ULN within 1 week.
[d] Two consecutive values >10 × ULN within concurrent muscle pain, tenderness, or weakness.

Laboratory abnormalities

In study 981-96, there was a dose-related increase in median change from baseline in ALT up to 6 U/L at the 80 mg dose. In addition, while no dose-related trend was observed, there was an isolated median decrease in platelet count of 18,500 per cubic millimeter in the 80 mg dose group. There was also a small increase in alkaline phosphatase up to 12 U/L at 80 mg. These same trends were seen for the entire placebo-controlled dataset discussed earlier. Also, as was seen for the pooled datasets, there was a dose-related increase in the number of patients with ALT >ULN, though no one had a clinically significant lab abnormality.

Conclusions:
In sum, though no novel safety issues were raised by study 981-96 with regard to crystalline atorvastatin, the small size of study 981-96, and in particular the limited exposure to atorvastatin 80 mg, does not permit any conclusions as to the safety of the drug, either on its own or in comparison to the amorphous form.

The 4-month safety update will include data from an open-label extension study comparing 80 mg crystalline to the equivalent amorphous dose and should yield a valid comparison between the two at least with regard to clinical lab abnormalities.

8.10 Effect of atorvastatin on adrenal steroid metabolism

Introduction

Adrenal steroidogenesis is proposed to utilize two sources of cholesterol. The first, and that required for acute increases in adrenal steroid production, for example under stress or in the setting of one-hour ACTH stimulation test, is the intracellular pool of cholesterol ester. The second source, required for maintenance of stimulated steroid synthesis, as in a 72-hour ACTH test, is cholesterol as part of LDL taken up by the adrenal cell via LDL receptors. Patients with hypo- and abetalipoproteinemia and with homozygous FH and absent LDL receptor function have reduced cortisol responses in 72-hour ACTH testing, supporting the role of uptake of LDL-C in prolonged stimulated adrenal steroid output.

The effect of HMGRIs on adrenal and gonadal steroidogenesis has been studied in the past, with an initial report suggesting an effect of simvastatin to decrease the peak cortisol response to ACTH. Other studies have failed to replicate this finding or to document impaired gonadal steroidogenesis in patients treated with simvastatin or pravastatin for up to 36 months.

In part because of the fact that the degree of LDL-C reduction seen in earlier studies with simvastatin, lovastatin, and pravastatin was only on the order of 30%, and because higher doses of atorvastatin effected significantly greater reductions in LDL-C, the current study was undertaken to investigate any effects of atorvastatin on adrenal function.

Design

Patients enrolled at one center of study 981-56 were studied. Recall that this was a 52-week, open-label study in patients with severe hypercholesterolemia, including heterozygous FH. The following describes the treatments of the 39 patients enrolled in the steroidogenesis study. Over the first 16 weeks of the trial, patients were titrated to 80 mg atorvastatin (N=18) or colestipol 10 g/day (N=21). Over the next 4 weeks, those patients not on atorvastatin 80 mg were titrated to combination therapy with either atorvastatin 40 plus colestipol 10 g (N=10) or simvastatin 40 mg plus colestipol 10 g (N=11). These treatments were maintained for the remainder of the 52-week trial.

All but four patients studied had heterozygous FH. Mean basal plasma cortisol levels were similar in all groups, as were the mean 30 and 60 minute post-ACTH levels at baseline.

Entry into the substudy required a basal AM cortisol level of >5 mcg/dl and ACTH response at 30 minutes to at least 18 mcg/dl with an increase of at least 7 mcg/dl above baseline.

The cortisol response to ACTH in a standard stimulation test was documented at baseline and at weeks 16, 36, and 52 of treatment. Patients reported to the clinic at 8:00am and underwent phlebotomy for protocol lab testing followed by ACTH testing. Blood was taken for basal cortisol determination, and after infusion of 25 mcg of cosyntropin, samples were collected at 30 and 60 minutes. Separate summary analyses (mean and standard error) of cortisol levels at each time point after ACTH for each of the 4 tests performed were presented by treatment group in the study report. In addition, the percent of patients developing an abnormal response by treatment group at each of the test weeks was also presented. *Post hoc* analyses included comparison of cortisol AUC for the baseline ACTH tests was compared to the AUCs for week 16, 36, and 52 ACTH tests.

Results

Only one patient had an abnormal response to ACTH. At 16 weeks, when the patient had been on only colestipol, he had a <7 mcg/dl increase in cortisol at 30 minutes and a 37% decrease from baseline at 60 minutes. The table below summarizes the ACTH testing data by treatment group in this study.

TABLE 8.10.1. Descriptive Summary of Mean Cortisol (SE)

Treatment Group/Dose	N	Week	Mean Cortisol (SE) at Time 0		Mean Cortisol (SE) at 30 Minutes		Mean Cortisol at 60 Minutes	
Atorvastatin 40 mg	18	0	20	(1.6)	43	(1.9)	47	(1.9)
Atorvastatin 80 mg	18	16	18	(1.7)	39	(1.7)	46	(1.7)
Atorvastatin 80 mg	16	36	21	(1.8)	41	(1.7)	47	(1.5)
Atorvastatin 80 mg	16	52	22	(2.3)	42	(2.2)	48	(2.3)
Colestipol 20 g + Simvastatin 0 mg	11	0	17	(1.9)	39	(1.8)	44	(1.8)
Colestipol 20 g + Simvastatin 0 mg	11	16	21	(3.2)	42	(2.0)	44	(2.3)
Colestipol 20 g + Simvastatin 20 mg	11	36	20	(2.7)	43	(2.6)	49	(2.7)
Colestipol 20 g + Simvastatin 40 mg	11	52	21	(2.3)	42	(2.4)	48	(2.7)
Colestipol 20 g + Atorvastatin 0 mg	10	0	17	(1.3)	39	(1.4)	45	(1.3)
Colestipol 20 g + Atorvastatin 0 mg	9	16	15	(2.0)	38	(1.6)	43	(2.2)
Colestipol 20 g + Atorvastatin 20 mg	10	36	15	(1.5)	39	(1.3)	45	(1.5)
Colestipol 20 g + Atorvastatin 40 mg	10	52	18	(1.6)	41	(1.1)	47	(1.3)

There are no trends over time in any of the treatment groups suggesting an adverse effect of any therapy on the cortisol response to ACTH.

The table below shows the mean cortisol AUCs for the ACTH tests performed at weeks 0, 16, 36, and 52. Though the baseline value for the group randomized to atorvastatin alone (forced titration to 80 mg by week 16 was statistically significantly greater than the 16-week value, no trend existed after that point.

TABLE 8.10.2. Cortisol AUC Values After ACTH Test

Treatment Group	N	Week	Mean (SE) AUC	
Atorvastatin 40 mg QD	18	0	2296	(102)
Atorvastatin 80 mg QD	18	16	2137	(94)[b]
Atorvastatin 80 mg QD	15	36	2241	(92)
Atorvastatin 80 mg QD	16	52	2317	(125)
Colestipol 10 g + Atorvastatin 0 mg	10	0	2116	(74)
Colestipol 20 g + Atorvastatin 0 mg[a]	9	16	2009	(85)
Colestipol 20 g + Atorvastatin 20 mg[a]	10	36	2063	(62)
Colestipol 20 g + Atorvastatin 40 mg[a]	10	52	2206	(54)
Colestipol 10 g + Simvastatin 0 mg	11	0	2089	(98)
Colestipol 20 g + Simvastatin 0 mg[a]	11	16	2221	(104)
Colestipol 20 g + Simvastatin 20 mg[a]	11	36	2335	(150)
Colestipol 20 g + Simvastatin 40 mg[a]	11	52	2294	(141)

AUC = Area under the curve

[a] Forced titration to colestipol 20 g at Week 4, atorvastatin or simvastatin 20 mg QD at Week 16 and 40 mg at Week 20

[b] Compared to Week 0 value, paired t test $p < 0.05$

Discussion

The study report offers an interesting explanation for the lack of effect of atorvastatin and other HMGRIs on adrenal steroid reserve as measured in the ACTH test. On the one hand, these drugs do not fully inhibit HMG-CoA reductase such that residual cholesterol biosynthesis may exist. Secondly, in patients with LDL receptor function, HMGRIs induce increased expression of surface receptors and thus augment cholesterol uptake. Third, most of the action of these drugs is in the liver and not in the periphery. One further explanation relates to a recently described "docking" receptor for HDL on steroidogenic tissue which provides an avenue by which HDL-C can be delivered to these cells as substrate for steroidogenesis. Such a mechanism is unlikely to be affected by HMGRIs.

Conclusions

The data reviewed reveal no adverse effect of high-dose, long term treatment with atorvastatin on adrenal reserve.

8.11 Drug-disease, drug-demographic, and drug-drug interactions

The following section summarizes the sponsor's probing for differences in the safety and tolerability of atorvastatin as a function of underlying disease, demographic variables, or concomitant medications.

Patients with and without hypertension
The overall incidence of adverse events and of associated adverse events was similar in patients receiving antihypertensive medication (N=776) and those not (N=1726). The rate of serious adverse events was increased in the former group, due to the increase in cardiovascular events.

In sum, the differences in the adverse event profiles between the two groups was consistent with the risks associated with hypertension.

Patients receiving or not receiving medication for the treatment of NIDDM
The overall incidence of all adverse events and of associated adverse events was similar between these two groups. The group receiving treatment for NIDDM had 3-fold higher rates of associated metabolic and nutritional disorders as well as higher rates of endocrine disorders, including hyperglycemia. The group not receiving NIDDM medications had twice the frequency of associated GI adverse events. The rate of serious adverse events was increased in the patients receiving treatment for NIDDM (N=140), though none were associated adverse events. Among the 2362 patients not receiving NIDDM medications, there were 7 deaths. There were no deaths in the other group.

In sum, the differences in the adverse event profiles between the two groups was largely consistent with the clinical consequences of NIDDM.

Patients with normal or abnormal renal function
The overall incidence of all and associated adverse events, of minor elevations in ALT, AST, and CPK were similar in patients with normal BUN or creatinine (N=2080) and those with BUN or creatinine >ULN (N=422).

Patients with (N=718) and without (N=1784) prior exposure to HMGRIs
There were no significant differences in adverse events between these two groups.

Patients with and without concurrent exposure to digoxin
Coadministration of digoxin and atorvastatin increased digoxin steady-state levels by ~20% in 12 subjects studied. Forty-two patients in the clinical studies were receiving concurrent digoxin and atorvastatin therapy. One patient was hospitalized for a pacemaker insertion and no unusual conditions were noted. In short, there are no data to suggest a clinically significant interaction between digoxina and atorvastatin, though the increase in digoxin levels with administration of atorvastatin is potentially important.

Atorvastatin exposure in children
In study 981-80, 9 children (≤14 years of age) received atorvastatin up to 80 mg/day for 8 weeks. There were no unusual side effects, serious adverse events, or clinically important laboratory abnormalities. In short, data are lacking as to the safety and tolerability of atorvastatin in children.

8.12 Four month safety update:

Scope of the safety summary

The four-month safety update was submitted on 10-17-96. The scope of the updated safety summary with regard to the clinical studies of atorvastatin includes those patient data originally summarized in the NDA submission of June 17, 1996: 2502 atorvastatin-treated patients in 21 completed clinical studies and an additional 2313 participating in ongoing studies as of March 15, 1996, 751 of whom were newly exposed to atorvastatin. All told, the integrated safety summary of the original NDA encompassed 3253 atorvastatin-treated patients. The new clinical safety information in the current submission includes data from 16 patients completing a single clinical study in the interim and data from 3334 patients in ongoing studies (including these 16), 1018 of whom were new exposures since the NDA was filed. Thus, the total exposure to date is 4271 patients. I have not addressed the subjects exposed in clinical pharmacology studies, as their exposures were very short and as the adverse event profile of the drug was similar in these 626 subjects as it was in the patients treated with atorvastatin. The table below summarizes the exposure to atorvastatin overall in clinical pharmacology and clinical studies.

TABLE 8.12.1. Number of Patients and Cutoff Dates for Safety Summaries in the NDA and 4 Mo-SU

	Clinical Pharmacology Studies			Clinical Studies		
	Received Atorvastatin	New Exposures	Data Cutoff Date[a]	Received Atorvastatin	New Exposures	Data Cutoff Date[a]
NDA						
Completed	590	590	01/01/96	2502	2502	01/01/96
Ongoing	0	0	–	2313[a]	751	03/15/96
TOTAL	590	590	01/01/96	NA	3253	03/15/96
4 Mo-SU						
Completed	36	36	04/30/96	16	0	04/30/96
Ongoing	0	0	–	3334[b]	1018	07/30/96
Subtotal	36	36	04/30/96	NA	1018	07/30/96
TOTAL	626	626	04/30/96	NA	4271	07/30/96

NA = Not appropriate because summing would double-count patients.
[a] Total includes patients from completed trials who subsequently entered ongoing extension studies.
[b] Total includes 16 patients from completed Study 981-039 who entered ongoing extension Study 981-074.

In addition to the overall summary of the safety data from these additional exposed patients, the safety update addressed two other issues. It compared the safety profile of the drug in the first and second years of exposure in a cohort of patients treated originally in study 981-08 and then subsequently in the open-label extension study 981-62. All told nearly 700 patients on doses of 10 and 20 mg were followed for two years. In addition, in the follow up to study 981-56 in severe hypercholesterolemics, study 981-77, the safety data for about 120 patients treated for more than a year and a half with amorphous atorvastatin 80 mg were compared to those from 224 patients treated for nearly a year with crystalline 80 mg atorvastatin.

Clinical safety data overview

Deaths
As was the case for the 15 deaths reported in the original NDA (10 of which were in atorvastatin-treated patients), none of the additional 9 deaths reported between March 16 and July 30, 1996 (4 in atorvastatin treated patients) was considered related to treatment. Again, most of the deaths were due to cardiovascular causes.

Non-fatal serious adverse events
Among the 3334 patients receiving atorvastatin between March 15, 1996 and July 30, 1996, 54 (2%) reported 63 serious adverse events, 39 of those patients for the first time. There were no differences in the type, incidence, or distribution of such events when compared to the original NDA data.

One patient had a serious adverse event considered related to therapy. This was a 70 year old Japanese women with multiple medical problems including history of CVA, TIA and dizziness, who experienced dizziness in association with atorvastatin treatment.

Carcinomas
14 carcinomas were newly diagnosed from the NDA cutoff date to July 30,1996. Five were diagnosed during the baseline period, 6 in patients receiving atorvastatin, 2 in patients receiving lovastatin, and 1 in a simvastatin-treated patient. The type and distribution of cancers were not different than what was seen in the original NDA and consistent with the demographics of the study population.

Withdrawals
Among the 16 patients enrolled in the only study to be completed since the NDA cutoff date, there were no additional withdrawals for any reason.

Clinically important transaminase elevations
In the original NDA submission, 39 patients with clinically important elevations in ALT were reported. Twenty-five were from completed studies and 10 from ongoing studies. Since the cutoff date for the NDA, 4 additional patients had such elevations, 3 on atorvastatin, 1 on lovastatin. The table below summarizes all of the reported clinically important transaminase elevations thus far in clinical studies:

TABLE 8.12.2. Overview of Clinically Important Transaminase Elevations
[Number (%) of Patients]

Treatment	NDA (Through March 15, 1996)	4 Mo-SU (March 16 - July 30, 1996)
Placebo	1	0
Atorvastatin (mg QD)		
10	3	0
20	2	0
40	4	0
80	17	3
40 + Colestipol	1	0
Lovastatin (mg QD)		
20	2	0
40	1	0
80	1	1
Fluvastatin (mg QD)		
20	1	0
Colestipol (g)		
20	1	0
Fenofibrate (mg/day)		
30	1	0
Total Patients	35	4

The incidence of clinically important ALT elevations among atorvastatin-treated patients was clearly dose-related in the original NDA with an incidence of 3.4% (13/383) in the group treated with 80 mg in completed studies. With the addition of 11 more cases from the data available up to October 10, 1996 and encompassing the one additional completed study and 6 ongoing studies, the incidence still appears dose related with an overall incidence of 2.3% in the 80 mg group. The table below summarizes these data.

TABLE 8.12.3. Incidence of Clinically Important ALT or AST Elevations

Dose mg QD	NDA: All Completed Studies			4 Mo-SU[a]		
	Number of Patients Exposed	Number (%) of Patients With Elevation		Number of Patients Exposed[b]	Number (%) of Patients With Elevation	
10	1677	2	0.1	1843	3	0.2
20	753	0	0.0	892	2	0.2
40	493	4	0.8	811	5	0.6
80	383	13	3.4	888	20	2.3
All doses	2502[c]	19	0.8	4271[c]	30	0.7

[a] Information in database as of October 10, 1996.
[b] Patients in extension Studies 981-062 and 981-077 were only counted if their dose was different from the dose they were exposed to in their initial Study 981-008 or 981-056, respectively.
[c] Patients may have been exposed to more than 1 dose; therefore, total patients exposed is not additive.

Through July 30, 1996, in completed and ongoing studies, over 50% of clinically important transaminase elevations among atorvastatin-treated patients have occurred in the first 16 weeks of treatment, and over 80% within the first 36 weeks. All told, 12 of 30 patients have ultimately discontinued treatment because of persistent LFT elevations.

CPK elevations
Thus far, there have been no atorvastatin-treated patients with clinically important CPK elevations defined as two consecutive measurements >10 x ULN 4 to 10 days apart with symptoms consistent with myopathy.

Overdosages
Thus far, there have been three exposures to atorvastatin 120 mg worthy of note. The first, reported in the NDA, was a patient in a clinical pharmacology study who mild nausea and jittery feelings immediately following the administration of a single dose of 120 mg atorvastatin. At 1.5 hours postdose, the subject reported feeling mildly giddy and euphoric and experienced mild mental confusion. At 4.5 hours postdose, he reported mild trouble chewing. All symptoms resolved spontaneously within 4.5 hours of onset. During a scheduled physical examination 4 hours postdose, the subject was unable to perform serial subtraction and had impaired short-term memory; no perceptual deficits were noted. Upon repeat examination 1 hour later, these symptoms had resolved. At the time, it was determined that all events were related to study medication and may in fact be considered dose-limiting.

The second instance was a patient, (patient 202, study 981-56, center 017) exposed to 120 mg atorvastatin for 29 days intermittently over a 54-day period. The patient, a white man with a history of hyperlipidemia, was randomized to atorvastatin 80 mg/day. The patient was dispensed 40 mg tablets of atorvastatin and was told to take 2 tablets once daily. The patient was compliant

with the dosing regimen through Visit 7. When the patient returned for his Visit 9, he stated that he took 3 tablets daily rather than 2 intermittently over a 54-day period between Visits 7 and 9 but could not recall the specific days he took additional tablets. At this time, full chemistry and lipid panels were drawn with all values within an acceptable range. The patient's LDL-C decreased by 60% from baseline values. The patient reported no unusual side effects during this 54-day period. For the remainder of the study, the patient took medication as instructed and no clinically important laboratory abnormalities or serious adverse events were reported.

Patient 007 (Study 981-080, Center 008) was exposed to atorvastatin 120 mg/day for 43 days. The patient, an 84.7 kg, white man who has been identified as heterozygous for familial hypercholesteremia in addition to Type III dysbetalipoproteinemia began treatment with atorvastatin 40 mg/day and titrated up to 80 mg/day under the compassionate use protocol. The patient was dispensed 40-mg tablets of atorvastatin at Visit 3 and was told to take 2 tablets once daily. The patient called the investigator prior to his next scheduled visit to report that he did not receive enough medication. After querying the patient it was discovered that he had inadvertently taken 3 tablets daily rather than 2 for 43 days between Visits 3 and 4. The patient was seen for an interim visit, at this time a full chemistry and lipid panels were drawn with all values within an acceptable range. The patient's LDL-C decreased by 39% from baseline values. The patient reported no unusual side effects during this period. Currently, the patient remains in the study and has resumed taking his medication as instructed and no clinically important laboratory abnormalities or serious adverse events were reported.

Conclusions
In summary, the overall profile of atorvastatin with regard to adverse events and laboratory abnormalities is not altered by the additional data obtained in the interim between the cutoff for the original NDA submission and the cutoff for this 4 month safety update.

Study 981-08/62: comparison of safety profiles in patients over 1st and 2nd year of exposure (10 and 20 mg)

Study 981-08 was a 52 week dose-titration study in which one group of patients received atorvastatin 10 or 20 mg and the other group lovastatin 20 or 40 mg for at least the last 30 weeks of the study. Patients completing 981-08 could enter a one-year, open-label, dose-titration extension study and receive atorvastatin 10 to 80 mg or lovastatin 20 to 80 mg. This allows for the comparison of the experience of a cohort of patients over the first and second years of exposure to atorvastatin. All told, there were 719 atorvastatin-treated patients (662 patient-years, mean days on drug 343) in 981-08. Of 640 patients completing this study, 623 continued on atorvastatin in 981-62 (total 1232 patient years, mean days on drug 722). Ninety-seven percent completed at least 21 months of atorvastatin therapy and 80% completed at least 24 months by the cutoff date for the safety update. There were 193 lovastatin-treated patients in 981-08 and 164 in 981-62. The sponsor's analyses compared the experience among these four groups to the experience reflected in the 1-year studies data grouping from the original NDA safety summary.

Adverse events
There were no significant differences in type, incidence, or frequency distribution within body systems of adverse events between the first and second years of exposure. Likewise, for associated adverse events, the type, frequency distribution, and incidence was similar from the first to second years of exposure in the atorvastatin group and not different from that seen in the

1-year studies grouping across treatment groups or from the first and second year's exposure to lovastatin.

Deaths
There were no additional deaths in 981-08 or 981-62.

Serious adverse events
There was no differences between years 1 and 2 of exposure in the type, incidence, and frequency distribution across body systems for serious adverse events.

Cancer
Cancer incidence, type, and frequency distribution were not different between the first and second years of exposure.

Withdrawals
Withdrawal rates were decreased in the second year of exposures for both atorvastatin and lovastatin.

Lab abnormalities
The spectrum, incidence, and frequency distribution of lab abnormalities was similar in the atorvastatin and lovastatin-treated patients for the first and second years of exposure, and overall similar across the different treatments. The rate of clinically important ALT elevations was also similar for the two years of exposure to atorvastatin. None of the 28 patients in this cohort exposed to atorvastatin 80 mg in the second year developed a clinically important LFT abnormality.

There were no clinically important CPK abnormalities in 981-08 or 981-62. A summary of maximum CPK elevations by dose in study 981-62 appears in the table below. Clearly, there is no evident dose-dependent effect on the incidence of maximum CPK levels in any of the ranges listed. No conclusions can be drawn from the single case of an elevation to greater than 3 times the upper limit of normal in the small 80 mg group.

Table 8.12.4. Summary of CPK elevations in study 981-62 by atorvastatin dose

Dose	N*	>3≤5 x ULN	>5≤10 x ULN	>10 x ULN
10	412	4 (1)	2 (<1)	1 (<1)
20	119	0 (0)	0 (0)	0 (0)
40	74	0 (0)	0 (0)	0 (0)
80	13	1 (8)	0 (0)	0 (0)

*Number of patients is the number whose maximum elevation was at the dose indicated, not total number receiving that dose.

Conclusions
The second year of exposure to atorvastatin produced no novel adverse events, no increase in the rate of specific clinical or laboratory adverse events in this cohort of patients treated with 10 and 20 mg of atorvastatin. No changes in the overall safety profile of the drug occurred during the second year of follow up.

Comparison of 80 mg amorphous vs 80 mg crystalline atorvastatin
In the original NDA submission, in the completed studies dataset, there were data included for fewer than 15 patients treated in study 981-96 with crystalline atorvastatin 80 mg for up to 6 weeks. The current submission summarizes data from 981-77 comparing the safety profile of 80 mg amorphous atorvastatin in 116 patients to that of 80 mg crystalline atorvastatin in 224 patients over at least 1 year of follow up. Patients completing 981-56 were randomized to either crystalline or amorphous atorvastatin starting at 40 mg in study 981-77. Dose was increased to 80 mg in the majority of patients after 8 weeks. Adverse events continuing from 981-56 were counted again in 981-77 and attributed to randomized treatment.

The exposure to amorphous drug was 184 patient years (mean days on drug = 578). Exposure to crystalline drug was 221 patient years (mean days on drug = 360).

Adverse events
The all and associated adverse event profiles for the two drug forms were similar with the most frequent associated adverse events being gastrointestinal and musculoskeletal in origin. Five percent of the patients taking crystalline drug complained of myalgia as compared to none taking amorphous atorvastatin, though none withdrew because of this event. The incidence of GI and nervous system associated adverse events was not different between the two groups.

Deaths
Throughout 981-77 there have been 2 deaths, both in the amorphous atorvastatin group. The incidence of withdrawals due to adverse events is similar in the two groups, between 2 and 3 percent. In the crystalline group, the four withdrawals, one each, were due to diarrhea, abdominal pain, abnormal LFTs, and pharyngitis.

Labs
The spectrum, incidence, and frequency distribution for the two groups was similar and shown in the table below.

TABLE 8.12.5. Study 981-077: Comparison of Clinical Laboratory Abnormalities While Receiving Amorphous or Crystalline Atorvastatin
[Number (%) of Patients]

Laboratory Parameter	Criteria	Atorvastatin Amorphous N = 116		Atorvastatin Crystalline N = 224	
ALKPHOS	>3.00 × ULN	0	(0)	3	(1)
ALT	>ULN	55	(47)	101	(45)
AST	>ULN	52	(45)	76	(34)
CPK	>5.00 × ULN	1	(1)	2	(1)
GLUC	>1.25 × ULN	7	(6)	4	(2)
	<0.75 × ULN	0	(0)	0	(0)
LDH	>2.00 × ULN	1	(1)	0	(0)
TBILI	>1.50 × ULN	5	(4)	6	(3)

Clinically important ALT elevations
The table below summarizes the clinically important ALT/AST elevations by drug form and dose

in 981-77. Two of the patients randomized to crystalline atorvastatin, one receiving 20 mg and the other 40 mg, had previously had clinically important ALT elevations while receiving amorphous atorvastatin. When these two patients are excluded, there is no difference in the overall incidence of clinically important ALT elevations between the two groups (2%).

TABLE 8.12.6. Study 981-077: Comparison of the Number of Patients With Clinically Important ALT/AST Elevations While Receiving Amorphous or Crystalline Atorvastatin

Dose	Amorphous Atorvastatin N = 116	Crystalline Atorvastatin N =224
20[a]	0	2[b]
40[a]	1	1[b]
80[a]	1	4
All Doses	2 (2%)	7[b] (3%)

[a] Number of patients exposed to each dose is not available; therefore, percentage of patient with event by dose cannot be calculated. Total number of patients across all doses was 116 for amorphous and 224 for crystalline atorvastatin.

[b] Two patients, 1 receiving crystalline atorvastatin 20 mg the other 40 mg QD, had experienced a clinically important ALT AST elevation in the prior double-blind comparison Study 981-056 while receiving amorphous atorvastatin.

As was the case in the original NDA submission, there were no sequelae of any of these elevations.

The table below summarizes the maximum transaminase elevations by dose in study 981-77, and shows no differences between the two dosage forms in the incidence of maximum transaminase levels within any of the ranges listed.

Table 8.12.7. Summary of maximum transaminase levels by dose. Study 981-77

Dose	Number of patients[a]	< 1 x ULN	>1≤2 x ULN	>2≤3 x ULN	>3 x ULN
Amorphous					
0[b]	3	1 (33)	0 (0)	1 (33)	1 (33)
20	1	0 (0)	1 (100)	0 (0)	0 (0)
40	7	3 (43)	2 (29)	2 (29)	0 (0)
80	105	55 (52)	44 (42)	4 (4)	2 (2)
Crystalline					
0[b]	1	1 (100)	0 (0)	0 (0)	0 (0)
20	2	0 (0)	0 (0)	0 (0)	2 (100)
40	28	18 (64)	9 (32)	0 (0)	1 (4)
80	193	99 (51)	80 (41)	10 (5)	4 (2)

[a] Number of patients is the number of patients whose maximum level was at the dose indicated, not number of patients who received that dose
[b] Patient of 0 dose at time of event

There were no important CPK elevations during study 981-77. A summary of maximum CPK elevations by dose in this study (not shown) shows no differences between amorphous and crystalline atorvastatin groups in the incidence of CPK levels within any of the ranges examined (>3≤5 x ULN, >5≤10 x ULN, >10 x ULN). In both groups, CPK elevations of any degree above 3 X ULN are rare, occurring in 1 to 2% of patients.

Conclusions

In 981-77, in which patients were randomized to receive 80 mg of either crystalline or amorphous drug, the overall safety profile of crystalline atorvastatin appeared similar to that of the amorphous form. There appears to be no difference in the incidence of either minor or clinically important LFT or CPK abnormalities between the amorphous and crystalline groups. Furthermore, no novel toxicities were observed in association with crystalline drug. This study is an adequate bridging safety study for crystalline atorvastatin.

9.0 Labeling review
This review of the labeling for atorvastatin will include comments under each section heading of the sponsor's proposed label, as well as specific deletions and insertions recommended by this reviewer. The proposed label with redline and ~~strikeout~~ corresponding to the recommendations in this section is attached to the review. The page and line numbers in the review correspond to those in the attached revised label. In addition to the changes recommended by this reviewer, the attached label contains revisions recommended by the other disciplines involved in the review of this NDA and not commented on in this review.

Description
No comments.

Clinical Pharmacology section
Mechanism of action

line 38
Insert **"In animal models,"** at the beginning of the paragraph.

line 42
The third sentence of the paragraph states that

It is not supported by data in the NDA and should be deleted.

This statement is based on a lipid turnover study (981-76) in 6 patients with mixed dyslipidemia. The study was a 20-week, open-label, randomized, crossover design which was intended to investigate the lipid altering mechanism of action of atorvastatin 40 mg as compared to that of simvastatin 40 mg.

This study was not reviewed in the main body of the NDA review. No primary data from this study were provided in the NDA. The study report is inadequate, indeed contradicting the protocol in stating the dose of atorvastatin as 10 mg. The study was originally powered based on an anticipated 12 patients. Of the 6 who were enrolled, the data presented in the study report show that only 4 of 6 had data on both drugs. Furthermore, the only data presented are individual patient data, with no statistics performed on data grouped by treatment. The abstract states a 37% mean reduction in TG on atorvastatin as compared to a 35% reduction on simvastatin, without any testing of statistical significance. Likewise, Apo B was reportedly reduced 48% in the atorvastatin group versus 40% in the simvastatin group, again without statistical testing. In short, the data appear not to support the above statement in labeling. It should be deleted.

line 44
The fourth sentence refers to the efficacy data in FH homozygotes and states that "LIPITOR reduces LDL-C in patients with homozygous FH..." Not all patients of the relatively small group studied responded to therapy. Specifically, of 24 patients treated for at least 4 weeks in study 981-80, 5 (21%) had not responded to therapy by the time of preparation of the study report. Overall, in 981-54 and -80, of 30 total patients treated, 25 had responded to therapy with at least a 10% lowering of LDL-C from baseline. The statement should be qualified by changing the sentence to read as follows:

LIPITOR reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

lines 47-70
The inclusion of broad summary statements addressing certain demonstrated clinical benefits of lipid lowering, of summary data from the LRC-CPPT using cholestyramine, and of descriptions of the 4S and WOSCOPS trials and their results in the label for atorvastatin goes counter to 21 CFR 201.56, and they should be deleted. Such information is not essential for the safe and effective use of the drug. Furthermore, the inclusion of this information implies effectiveness of atorvastatin not demonstrated in well-controlled trials using the drug. At this point in time, there is sufficient general knowledge as to the presumed benefits of cholesterol lowering such that no explicit rationale need be provided in labeling. Finally, the inclusion in the labels of all the lipid lowering agents of the NCEP guidelines itself provides the relevant information necessary for the identification of the appropriate treatment populations for these drugs and for the determination of individualized treatment goals. These guidelines, in addition to information in each label pertaining specifically to the labeled drug, provide sufficient information for the safe and effective use of each agent. At present, the claims of effectiveness with regard to clinical endpoints of certain of the HMGRIs are exclusive and reserved for the individual drugs for which such effectiveness has been clearly demonstrated in clinical trials.

line 71
The first sentence refers to the action of LIPITOR in **"in both subjects and in patients with..."** This reference to the observed effects in clinical pharmacology studies seems to contribute little in the way of important information for the safe and effective use of the drug and should be deleted. Revised language follows:

LIPITOR reduces total-C, LDL-C, and apo B in patients with ...

line 74
The sentence beginning **"In animal models..."** summarizes data from studies in animals on the effects of atorvastatin on the progression and regression of atheromata. This information is not essential to a description of the biochemical and/or physiological mode of action of the drug in humans and furthermore has not been shown in well-controlled clinical trials to be pertinent to the clinical use of atorvastatin (21 CFR 201.57). It should be deleted.

line 76
The disclaimer as to the clinical effects of lipid lowering with atorvastatin which begins **"Although cardiovascular events..."** again seeks to imply potential effects of atorvastatin on cardiovascular morbidity and mortality and on total mortality. To the extent that such effects remain to be demonstrated, this statement should be deleted and should be replaced with a separate paragraph which should read as follows:

The effect of LIPITOR-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity and mortality has not been determined.

This is the format of similar statements that have appeared in the labels for other lipid lowering therapies not proven to have beneficial effects on clinical outcomes.

Pharmacodynamics

No comments.

Pharmacokinetics and drug metabolism
No comments.

Special populations
No comments.

Clinical Studies
line 149
In the interest of consistency with the labels for other lipid lowering agents, and to avoid confusion, it is recommended that identification of study and target populations for atorvastatin include Fredrickson classifications in addition to the nomenclature proposed by the sponsor. The heading on this page should read:

Hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Types IIa and IIb).

line 155
The sentence beginning **"LIPITOR is effective in a wide variety of patient populations..."** makes too sweeping a statement about the effectiveness of atorvastatin in young patients. The only pediatric patients receiving atorvastatin in the NDA database were fewer than five children with homozygous FH. The sentence should be changed as follows:

LIPITOR is effective in a wide variety of patient populations with hypercholesterolemia, with and without hypertriglyceridemia, in men, women, and in the elderly.

line 158
The sources of the placebo-controlled efficacy data by dose should be the group of studies from which pooled data demonstrate statistically significant changes in lipids when compared to placebo. These pooled data better reflect the true effect of the drug in these patients. Suggested language is as follows and the revised table 1 appears below:

In a multicenter, placebo-controlled, in patients with hypercholesterolemia, LIPITOR given as a single daily dose reduced total-C, LDL-C, apo B, and TG (Table 1).

Table 1. Mean percent change from baseline. Studies 981-C4, 981-08, 981-10, 981-25, 981-96 combined

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	347	-7%	-10%	-7%	-1%	+3%	-11%
10	1476	-27%	-37%	-29%	-17%	+7%	-38%
20	20	-33%	-43%	-36%	-28%	+10%	-42%
40	77	-34%	-47%	-39%	-23%	+9%	-46%

60	13	-40%	-51%	-41%	-35%	+3%	-50%
80	78	-42%	-55%	-46%	-33%	+7%	-53%

The inclusion in the table of data from 13 patients receiving 60 mg atorvastatin daily in study 981-96 serves to illustrate the dose-response for LDL-C lowering. To the extent that this dose is not proposed for use by the sponsor, it may not be essential information.

line 177

The tables summarizing the trials comparing atorvastatin 10 mg to the "starting" doses of lovastatin, simvastatin and pravastatin should contain mean changes in lipids from baseline and confidence limits for the differences in mean changes between treatments. This will more accurately convey the relative efficacies of the drugs studied. The introductory statement for the table should be revised as follows and a single summary table is shown below:

In three multicenter, double-blind studies in patients with hypercholesterolemia, LIPITOR was compared to other HMG-CoA reductase inhibitors. After randomization, patients were treated with atorvastatin 10 mg per day o a fixed dose of the comparative agent (Tables 2).

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ON ORIGINAL

Table 2. Mean percent change from baseline at endpoint. Double-blind randomized active controlled trials.

Treatment (dose)	Total-C	LDL-C	Apo B	TG	HDL-C	non-HDL-C /HDL-C
Atorvastatin (10 mg QD)	-27%	-37%	-28%	-16%	+7%	-37%
Lovastatin (20 mg QD)	-19%	-27%	-20%	-6%	+7%	-28%
95% CI for Diff	-9.2, -6.4	-10.7, -7.1	-10.0, -6.6	-15.2, -7.1	-1.7, 2.0	-11.2, -7.1
Atorvastatin (10 mg QD)	-25%	-35%	-27%	-16%	+6%	-36%
Pravastatin (20 mg QD)	-17%	-24%	-17%	-10%	+8%	-28%
95% CI for Diff	-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1

Atorvastatin (10 mg QD)	-29%	-37%	-33%	-22%	+7%	-39%
Simvastatin (10 mg QD)	-23%	-31%	-29%	-14%	+8%	-33%
95% CI for Diff[1]	-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

[1]A negative value for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin.

line 231

The first sentence of this paragraph referring to clinical studies comparing atorvastatin to other lipid altering agents is too broad and implies proof of superior efficacy of atorvastatin beyond that demonstrated in the comparative trials conducted. It should be deleted. Furthermore, qualifying statements about the limitations of the data presented should be included, particularly with regard to extrapolations to clinical outcomes and to relative lipid altering effectiveness of doses not compared in head-to-head studies. Finally, an explicit statement as to non-interchangeability of the statins is recommended.

The second sentence describing the pooled efficacy data from these trials and the percent of patients reaching NCEP goal is not supported by the data presented. Quite simply, studies 981-09 (atorvastatin vs. pravastatin) and 981-37 (atorvastatin vs. simvastatin) did not treat to NCEP goal, but rather fixed the goal LDL-C for all patients at 130 mg/dl. This statement should be deleted or revised accordingly.

The impact on clinical outcomes of the differences in lipid altering effects between treatments shown in Table 2 is not known. Studies comparing the lipid altering effects of atorvastatin 10 mg to those of higher doses of lovastatin, pravastatin, and simvastatin have not been done. The drugs compared in the studies summarized in Table 2 are not necessarily interchangeable.

line 242

The section describing the effects of atorvastatin in homozygous familial hypercholesterolemia should include the results of study 981-54 and 981-80 but should be restricted to the discussion of the results in the patients with proven homozygous FH. The 11 patients with severe unresponsive hypercholesterolemia enrolled in 981-80 who did not have documented FH should be excluded. Revised language follows.

In uncontrolled studies 30 patients ages 6 to 37 years with homozygous FH who had ≤15% response to maximum combination drug therapy in the past received maximum daily doses of 30 to 80 mg of LIPITOR. Twenty-five patients had a reductions in LDL-C ranging from 11% to 53% (mean__%). In 5 patients with absent receptor function, mean LDL-C reduction was 13.6%. Five patients had less than a 10% response to treatment.

Indications and usage
line 254
The language of the indication for use in primary hypercholesterolemia and mixed dyslipidemia should include Fredrickson class designations in order to be consistent with the labeling for other lipid lowering agents. Revised language follows:

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

line 257
The indication for use of atorvastatin in homozygous FH should clarify that therapy with atorvastatin should be as an adjunct to other lipid lowering modalities (i.e. apheresis) or if such modalities are unavailable. Clearly, atorvastatin is not effective enough in lowering LDL-C in these patients to warrant its use as first-line therapy. Revised language follows:

LIPITOR is indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid lowering modalities (e.g. LDL apheresis) or if such modalities are unavailable.

Warnings
Liver Dysfunction

line 304
Dose related increases in the incidence of LFT abnormalities, both moderate (≤3 x ULN, transient) and clinically important (>3 x ULN, persistent) were observed with atorvastatin therapy. This information, the nature of the moderate abnormalities, the number and percent of patients developing clinically important abnormalities, their disposition, the duration of exposure leading up to the abnormality or the distribution of all cases across time of exposure should be included. Finally, the percent of patients taking 80 mg atorvastatin developing such abnormalities should be cited to emphasize the increased risk at this high dose. The utility of including quantitative information about both types of LFT abnormality (moderate and clinically important) is to permit an assessment of the significance of the first appearance of a minor abnormality. These are predicted to occur commonly, and with increasing frequency at higher doses. The knowledge that of all minor abnormalities, only a small percentage will be harbingers of more severe hepatotoxicity requiring dose reduction or interruption or discontinuation of therapy is important and useful information for doctors and patients alike.

The sponsor recommends liver function testing at baseline, at 8 to 12 weeks and periodically (e.g. every 6 months) thereafter. This is based upon the observation that the largest number of cases (9) occurred between weeks 7 and 12. There were 2 cases that occurred by six weeks, as well as 6 cases that occurred between 13 and 18 weeks.

It is recommended, in the interest of consistency with the other agents in the class, and based upon the observations above, that initial testing be at 6 to 12 weeks, that repeat testing be performed at 18 weeks, that a similar algorithm be followed after elevation in dose, and that follow up LFT testing be performed semiannually thereafter. Bold type is recommended as shown and is consistent with the labeling for other statins. Revised language follows:

Elevations of serum transaminases do occur in association with atorvastatin therapy. In clinical trials of atorvastatin, the vast majority of these changes were moderate (≤3 x ULN), transient, and asymptomatic, and did not require interruption of treatment. Dose-related increases in the incidence of these minor transaminase elevations were observed, with nearly 40% of patients treated with 80 mg having a maximum ALT level >1 and ≤3 X ULN.

A small number of patients treated with atorvastatin in clinical trials (N=30, 0.7%) developed persistent elevations in serum transaminases to >3 x ULN. The incidence of these abnormalities was dose-related with 2.3% of patients treated with 80 mg experiencing such elevations. Over 50% of these elevations occurred in the first 16 weeks of treatment, and over 80% within the first 36 weeks. Increases were generally not associated with jaundice or other clinical signs or symptoms. On dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels. Most patients (18 of 30) continued treatment on a reduced dose of atorvastatin without sequelae.

Liver function tests should be performed before the initiation of treatment, at 6 to 12 weeks and again at around 18 weeks after initiation of therapy and increase in dose, and periodically (e.g. every 6 months) thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 × ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.

Skeletal muscle
The section on skeletal muscle effects of atorvastatin is satisfactory, though bolding is recommended as shown in the attached label. This is consistent with the labels for the other statins.

Precautions
line 415
The section on endocrine effects should include the "class" labeling with regard to potential effects on steroid metabolism, as follows:

However, clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration nor impair adrenal reserve. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG; the effect of atorvastatin on HCG-stimulated testosterone secretion has not been studied. The effects of HMG-CoA reductase

inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis of pre-menopausal women are unknown. Caution should also be exercized if an HMG-CoA reductase inhibitor is administered concomitantly with drugs (e.g. ketaconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

Adverse reactions
The table (Table 6) of adverse events reported in >2% of patients treated in placebo-controlled trials is acceptable.

line 568
Table 7, which compares the adverse events reported for atorvastatin-treated patients to those reported for HMGRI-treated patients in the three head-to-head comparative studies is not appropriate and should be removed. In general, the capacity of any pre-marketing database to establish either the absolute or relative safety of a drug is limited by the numbers of patients studied, the controlled conditions, and the duration of exposure. While the number of patients treated in trials submitted to this NDA is clearly sufficient to establish the efficacy of atorvastatin, and while the results of studies 981-08, -09, and -37 do demonstrate that the 10 mg dosse of atorvastatin was more effective in lipid altering than the doses of the other HMGRIs studied in the first periods of the trials, the data do not allow conclusions as to the relative safety of atorvastatin and pravastatin, lovastatin, and simvastatin. Indeed, only 316 patients total received one of the three marketed HMGRIs studied (193 lovastatin, 78 pravastatin, 45 simvastatin), so the data for any one of the three are severely limited. Furthermore, the data are skewed toward the lower end of the atorvastatin dosage range and toward the higher ends of the ranges for the comparator drugs, such that direct safety comparisons are potentially mislea ling. In sum, to compare in labeling the safety of the marketed agents (particularly in the form o' adverse experience reporting) to that of atorvastatin based upon three small studies is certain to be inaccurate and prone to misuse and abuse in promotion.

The listing of adverse events reported in clinical trials of atorvastatin and grouped using COSTART terms is acceptable.

Overdosage
No comments.

Dosage and administration
line 662
Again, the Fredrickson classification of dyslipidemias should be used in addition to more descriptive nomenclature.

A recommended starting dose of atorvastatin should be stated, and should be 10 mg once daily. The dosage range should be stated. A statement as to the effectiveness of atorvastatin in combination with a bile acid sequestrant should be included. There should also be a reference to WARNINGS: Liver dysfunction following the statement of dosage range and a reference to ADVERSE REACTIONS: Concomitant Therapy and to WARNINGS: Skeletal Muscle. Any statements about the dose-relatedness, timing, and duration of effect, about efficacy of atorvastatin 10 mg in lowering LDL-C to goal should be left in the Clinical Pharmacology section where the specifics of the clinical trials on which the information is based can be described.

In the dosage recommendations for FH homozygotes, the place of atorvastatin as an adjunct to other therapies should be restated.

Revised language follows:

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Types IIa and IIb)

The recommended starting dose of LIPITOR is 10 mg once daily. The dosage range is 10 to 80 mg daily (see WARNINGS: Liver Dysfunction)

LIPITOR can be administered as a single dose in the evening, with food. Therapy should be individualized according to goal of therapy and response (see *NCEP Guidelines*, summarized in Table 5). After initiation and/or upon titration of LIPITOR, lipid levels can be reanalyzed within 2 to 4 weeks and dosage adjusted accordingly.

Homozygous familial hypercholesterolemia

The dosage of LIPITOR in patients with homozygous FH is 10 to 80 mg daily. LIPITOR should be used as an adjunct to other lipid lowering modalities (e.g. LDL apheresis) in these patients or if such modalities are unavailable.

Concomitant therapy
Atorvastatin may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see WARNINGS: Skeletal Muscle for other drug-drug interactions).

Dosage in patients with renal insufficiency
No comments.

Section 10 Summary and conclusions

NDA# 20-702 includes preclinical and clinical data that support the proposed marketing of atorvastatin, a new HMGRI. All told, 4271 patients have been exposed to atorvastatin in clinical trials with exposures of almost 2 years across the dosage range of 10 to 80 mg daily. As of the 4-month safety update, 888 patients have received atorvastatin 80 mg, most of them for between 1 and 2 years. The exposure across the dosage range is satisfactory. It is anticipated that the bulk of the use of atorvastatin will be at the lower doses (10-20 mg).

This new molecular entity is uniquely potent in its efficacy in lowering total-C, LDL-C, and TG in patients with Types IIa, IIb, and IV hyperlipoproteinemia. Dose-related mean LDL-C lowering of up to 55 or 60% was observed in clinical trials. Individual patients had LDL-C lowering of over 70% on 80 mg daily. Atorvastatin is effective in patients with severe hypercholesterolemia, including heterozygous FH, and has variable effects in patients with homozygous FH. The sponsor has proposed indications for use in homozygous FH as well as in Types IIa and IIb patients. In addition, the sponsor has proposed inclusion in the label of data comparing the efficacy of atorvastatin with that of other HMGRIs from controlled, blinded, parallel group clinical trials.

As an inhibitor of HMG-CoA reductase, atorvastatin falls among the marketed HMGRIs in potency. Its unique efficacy evidenced in the clinical trials included in the NDA lies both in the doses administered and, it is hypothesized, in the specificity of the drug for the liver and its long duration of action there. Indeed, pharmacodynamic studies demonstrate that the lipid altering effects of the drug are not influenced by time of day administered or by administration in a divided dose regimen. The efficacy of the drug in lowering TG does suggest a mechanism of action that goes beyond those of the other members of the class, though this has not been clearly elucidated.

The efficacy of the drug is not in question. The sponsor has accumulated more than sufficient data to support claims of effectiveness in the populations targeted.

With regard to safety, several issues arise. While atorvastatin is acting as an HMGRI, a class of drugs with which there is a tremendous amount of experience worldwide, this new drug has been administered in doses more potent in lipid lowering than anything currently on the market. Whether this lipid lowering potency is accompanied by increased toxicity has been a central question. Specifically, is atorvastatin treatment associated with an increased incidence of known adverse effects of the statins and is it associated with any novel adverse effects? The other issue addressed by the sponsor and in the review is the safety of the crystalline, to-be-marketed form of the drug. The vast majority of the safety database in the original NDA submission was in patients treated with the amorphous form of the drug. The two are not, strictly speaking, bioequivalent, due to the increased Cmax observed for the crystalline form. Furthermore, the crystalline form appeared more toxic in a small number of dogs studied, though no new toxic reactions were observed.

Review of the safety data from the original NDA submission and from the 4-month safety update does not reveal any novel toxicities of atorvastatin as compared to the other HMGRIs. In addition, a 1-year comparison study of amorphous 80 mg to crystalline 80 mg did not show any safety differences between the two drug forms. The sponsor has investigated the effects of the drug on liver, muscle, eye, and adrenals in addition to monitoring patients for clinical adverse

events.

The spectrum and distribution of clinical adverse events reported in the atorvastatin-treated patients were similar to those seen in the patients taking other HMGRIs. There were no effects of atorvastatin treatment on adrenal function as measured in ACTH tests, or on the eye, measured both by the incidence of cataracts spontaneously reported or by changes in visual acuity and lenticular opacities studied in a single center of a controlled trial comparing the effect of atorvastatin and lovastatin.

Gastrointestinal complaints (e.g. diarrhea) and myalgia were not uncommon in the atorvastatin clinical database with absolute rates overall between 1 and 3 percent. Overall, atorvastatin and combined HMGRI patients complained more of these events than did placebo patients. In certain analyses, the incidence of diarrhea in the atorvastatin patients did appear dose-related.

There were no cases of marked, persistent, and symptomatic CPK elevations suggesting frank myopathy associated with atorvastatin therapy. There were no dose related changes in CPK levels, either moderate or marked. This is consistent with the known idiosyncratic nature of the rare myopathic effects of the class, excluding the known increased risk of myopathy with certain concomitant medications.

The most remarkable adverse effects of atorvastatin are related to liver function. Dose-related effects were observed in the incidence of both moderate, transient and of marked, persistent LFT elevations. Nearly 50% of patients treated with 80 mg atorvastatin had maximum ALT levels >ULN. The majority of these elevations were transient and required no intervention. A minority progressed to more serious elevations, with 0.7% (30/4271) of the total atorvastatin exposed population and 2.3% of those taking 80 mg developing ALT >3x ULN noted on 2 consecutive clinic visits 4 to 10 days apart. About half of the 30 patients were withdrawn from treatment because of persistent abnormal LFTs. No patient suffered sequelae of these events. LFTs reverted toward baseline on dose reduction of discontinuation.

No other safety issues arose in the clinical trials.

In summary, based on the results of the clinical trials of atorvastatin calcium, the safety and efficacy of the drug in doses of 10, 20, 40, and 80 mg daily in the proposed target populations has been satisfactorily demonstrated. In limited parallel group comparative trials, and based on historical data, atorvastatin appears to offer greater degrees of LDL-C and total-C lowering than marketed HMGRIs. In addition, it consistently lowers TG in patients with mixed dyslipiemia and isolated hypertriglyceridemia, an effect not seen with the other members of the class. Finally, the spectrum of adverse effects of atorvastatin is not different from that of the other HMGRIs, though the incidence of at least mild and moderate LFT elevations at the higher doses does appear to exceed that associated with the other members of the class at currently marketed doses. Whether this relationship holds for marked, persistent LFT elevations is not clear from the NDA database.

Section 11 Recommendations

Atorvastatin calcium tablets (NDA# 20-702) should be approved for marketing as proposed by the sponsor. Labeling recommendations have been incorporated into the sponsor's proposed label, attached.

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

David G. Orloff
11-6-96

concur:
Dr. Sobel

11-27-96

cc:
NDA 20-702
HFD-510

NDA 20-702 Safety Update submitted on October 17, 1996, was reviewed and included in the Medical Officer's Review dated November 6, 1996.

Statistical Review and Evaluation

OCT 2 4 1995

NDA #: 20-702/1P

Applicant: Parke-Davis Pharmaceutical

Name of Drug: LIPTOR (atorvastatin calcium tablets)

Indication: Lipid lowering

Documents Reviewed: Volumes 1.1, 1.2,1.165 to 1.216

Medical Input: David Orloff, M.D. (HFD-510)

This review is divided into 5 main sections:

I. Review of placebo-controlled clinical trials[1];
II. Review of active-controlled clinical trials;
III. Review of trials in patients with homozygous familial hypercholesteremia and
IV. Review of clinical trials using crystalline formulation of atorvastatin.
V. Reviewer's comments and labeling recommendations

Sections I-IV briefly describe the trials and present the efficacy results. All reviewer comments are reserved for Section V.

In all studies (except 981-38), the primary efficacy variable was % change from baseline in LDL-C at endpoint (last week on fixed dose treatment). The LDL-C results are presented in the tables along with the results for several other efficacy variables mentioned in the sponsor's proposed labeling. In addition, several safety variables were examined as suggested by the medical reviewer but only the results for ALT were considered important for presentation in the review. The ALT results are presented graphically at the end of each section.

For the majority of the trials, the primary analysis performed by the sponsor was analysis of covariance (ANCOVA) with baseline as the covariate at endpoint. In the study reports and in the labeling, the sponsor presented baseline-adjusted means, while in the tables presented here the unadjusted means are provided. This reviewer believes that the unadjusted means are more appropriate for describing the magnitude of response to be expected from atorvastatin. Nevertheless the values for the unadjusted and baseline-adjusted means are very close (not varying by more than 3%) and therefore the use of either mean is not an important issue for this application. In addition, the sponsor presented results by week and performed repeated measures analyses for some studies.

Due to the consistency of the results from study to study in this NDA and to the broad evidence of efficacy in this drug class, only a few statistical results were verified by this reviewer.

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[1] Study 981-08 had both an active control and placebo control arm and so it is included in both Sections I and II.

I. Review of Placebo-controlled Clinical Trials

Table 1 below summarizes the designs of the 5 placebo-controlled studies completed by the sponsor. In all studies, patients were instructed to follow the NCEP Step 1 diet and to keep dietary diaries. To enter the double-blind period, patients (with the exception of Study 981-25) needed a score on the Food Record Rating (FRR) scale of less than 15 (a score of 10 or less indicates compliance with the NCEP Step 1 diet). About ⅔ of the patients followed the prescribed diet (and had scores of 10 or less) during the baseline phase; during the treatment phase, compliance dropped to about 50% (these results were consistent across treatment groups within each trial).

The inclusion criteria for Studies 981-04, -08, -10 and -25 were similar regarding lipid levels (see Dr. Orloff's review for details)[1]. Study 981-38 was a study of patients with hypertriglyceridemia so the only lipid level requirement was that patients have a triglyceride (TG) of 350 mg/dL or greater.

Six doses of atorvastatin were tested for efficacy in these studies (2.5, 5, 10, 20, 40 and 80 mg daily given at bedtime). Most of the patients (see Table 2) were given 10 mg; the sponsor's recommended starting dose.

Table 1. Designs of Double-blind Randomized Placebo-controlled Trials

Study Number (Dates Conducted)	# of Centers (Locations)	Treatment Arms	Treatment Periods
981-04 (3/92-11/92)	6 (US and Canada)	Atorvastatin 2.5, 5, 10, 20, 40 and 80 mg QD Placebo	8 weeks baseline 6 weeks DB
981-08[2] (1/94-7/95)	31 (US)	Atorvastatin 10 mg QD Placebo Lovastatin 20 mg QD	6 weeks baseline 16 weeks DB
981-10 (3/94-3/95)	4 (US)	Atorvastatin 10 mg QD Placebo	6 weeks baseline 26 weeks DB
981-25 (8/94-2/95)	10 (US)	Atorvastatin 10, 40 and 80 mg QD Placebo	6 weeks baseline 16 weeks DB
981-38 (1/93-8/93) Pilot Study	8 (US and Canada)	Atorvastatin 5, 20 and 80 mg QD Placebo	4 weeks baseline 4 weeks DB

The treatment groups within each study were balanced with respect to demographics. The mean age of the patients was 57 years. More than 90% were over 40 and 27% were 65

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[1]In general, at randomization, LDL-C values needed to be above or equal to 160 mg/dL and less than about 250 mg/dL and Total TG needed to be less than or equal to 400 mg/dL.

[2]Study 981-08 was a 52-week study with 2 treatment periods; the first period of 16 weeks was a fixed dose period with patients treated as shown in the table (this period is the focus of this review). The second period of 36 weeks was designed to compare atorvastatin and lovastatin with no placebo arm.

or older. For Studies, 981-04 and 981-38, more than 80% of the patients were male, while for the other studies, about 60% were male. About ¼ of the patients had received reductase inhibitors before entering this trial.

Table 2 below shows the number of randomized patients in each study and the number of dropouts. Dropouts had no effect on the efficacy results since there were very few dropouts and nearly all the dropouts contributed data to the intent-to-treat analyses performed by the sponsor.

Table 2. Number of Patients Randomized (Number of Dropouts)
Double-blind Randomized Placebo-controlled Trials

Study	Placebo	Ator 2.5	Ator 5	Ator 10	Ator 20	Ator 40	Ator 80
981-04	12	11 (1)	13	11	10	12 (1)	12 (1)
981-08	133 (16)	X	X	708 (50)	X	X	X
981-10	19 (1)	X	X	20 (2)	X	X	X
981-25	56 (6)	X	X	58 (1)	X	57 (4)	57 (8)
981-38	14	X	13	X	16	X	13 (1)

About half the dropouts in each group discontinued the study due to an adverse event (ADE); the remainder dropped out for a variety of reasons including, primarily, patient decision or lost-to-follow-up. There was no evidence of a dose response relationship for incidence of ADE's.

The efficacy results of the placebo-controlled trials for 4 efficacy parameters (total cholesterol (TC), LDL-C, Apo-B and TG) are summarized in the following 4 tables. The protocol-specified primary efficacy variable in Studies 981-04, -08, -10 and -25 was percent change in LDL-C at the last week of double-blind treatment. The other variables were considered secondary variables. For Study 981-38, the primary efficacy variable was TG stratified by LDL-C at baseline (≤ 160 and > 160).

The endpoint results for TC (Table 3), LDL-C (Table 4) and Apo B (Table 5) showed that atrovastatin (at any dose) was more effective than placebo ($p \leq .0001$ for most comparisons). For the studies with multiple dose groups, Dunnett's test revealed significant differences for each dose compared to placebo. As seen from the tables below, a clear dose response is evident for all 3 efficacy measures; this was substantiated by significant trend test results.

The full magnitude of the mean response was reached by Week 4 in all 5 studies for TC, LDL-C and Apo B and was stable until the end of the trial. Repeated measures analyses revealed significant treatment differences for all 3 measures.

Table 3. Efficacy Results for Total Cholesterol at Endpoint (LOCF)
Double-blind Randomized Placebo-controlled Trials

Study	Placebo	Ator 2.5	Ator 5	Ator 10	Ator 20	Ator 40	Ator 80
981-04 Baseline % Change	267.1 +5%	262.6 -17%	267.1 -22%	281.8 -31%	278.2 -35%	271.0 -38%	267.6 -46%
981-08 Baseline % Change	276.6 +1%	X	X	276.6 -27%	X	X	X
981-10 Baseline % Change	275.2 +3%	X	X	270.9 -24%	X	X	X
981-25 Baseline % Change	309.1 +2%	X	X	285.4 -24%	X	279.7 -34%	288.3 -40%
981-38 Baseline % Change	262.3 -0.2%	X	253.2 -20%	X	288.9 -32%	X	263.6 -43%

Table 4. Efficacy Results for LDL-C at Endpoint (LOCF)
Double-blind Randomized Placebo-controlled Trials

Study	Placebo	Ator 2.5	Ator 5	Ator 10	Ator 20	Ator 40	Ator 80
981-04 Baseline % Change	184.7 +7.2%	182.8 -25%	185.6 -30%	196.2 -41%	196.1 -45%	185.6 -50%	189.7 -61%
981-08 Baseline % Change	191.6 +1%	X	X	192.0 -37%	X	X	X
981-10 Baseline % Change	195.2 +2%	X	X	187.7 -33%	X	X	X
981-25 Baseline % Change	222.7 +2%	X	X	202.0 -31%	X	199.3 -46%	206.4 -52%
981-38 Baseline[1] % Change	115.3 +1%	X	121.8 -14%	X	123.4 -31%	X	107.7 -39%

[1] In this study of patients with elevated triglycerides, there were no inclusion criteria regarding LDL levels.

Table 5. Efficacy Results for Apo B at Endpoint (LOCF)
Double-blind Randomized Placebo-controlled Trials

Study	Placebo	Ator 2.5	Ator 5	Ator 10	Ator 20	Ator 40	Ator 80
981-04							
Baseline	165.7	162.8	164.5	178.2	176.4	157.5	165.7
% Change	+6%	-19%	-23%	-35%	-37%	-41%	-51%
981-08							
Baseline	176.1	X	X	177.2	X	X	X
% Change	+3%			-28%			
981-10							
Baseline	174.9	X	X	174.4	X	X	X
% Change	+4%			-27%			
981-25							
Baseline	205.9	X	X	189.5	X	186.2	191.5
% Change	+2%			-27%		-39%	-45%
981-38							
Baseline	154.3	X	150.1	X	159.3	X	137.6
% Change	+1%		-16%		-32%		-41%

The results for triglycerides (Table 6) were less consistent across time and across studies compared to the other 3 efficacy measures. The magnitude of the response varied considerably over time (particularly in Studies 981-04 and 981-10); sometimes by more than 15%. There appears to be some evidence of a dose response relationship in Study 981-38 (this was not tested by the sponsor) but not in the other studies (a test for trend in Study 981-04 produced a p-value of .32). Repeated measures analyses performed in Studies 981-10 ($p = .38$) and 981-25 ($p < .001$) produced inconsistent results.

Table 6. Efficacy Results for Triglycerides at Endpoint (LOCF)
Double-blind Randomized Placebo-controlled Trials

Study	Placebo	Ator 2.5	Ator 5	Ator 10	Ator 20	Ator 40	Ator 80
981-04							
Baseline	170.3	154.1	179.9	192.1	210.1	171.3	158.2
% Change	+0.1%	-9%	-25%	-13%	-32%	-25%	-26%
981-08							
Baseline	175.5	X	X	179.0	X	X	X
% Change	+5%			-16%			
981-10							
Baseline	164.8	X	X	169.1	X	X	X
% Change	+17%			-17%			
981-25							
Baseline	192.4	X	X	179.2	X	166.1	172.1
% Change	+4%			-21%		-22%	-31%
981-38							
Baseline[1]	623.4	X	543.7	X	659.5	X	587.6
% Change	-6%		-25%		-31%		-43%

[1] Patients were required to have a total TG of 350 mg/dL or greater to enter this trial.

In the Integrated Summary of Efficacy , the sponsor presented subgroup results of LDL-C for a pooled dataset of all parallel group studies (a total of 22 studies). This reviewer repeated the sponsor's analyses by age, gender and race for the 5 placebo controlled trials presented here. Based on a guideline issued by FDA this reviewer defined 65 years as the cutoff for a geriatric population (the sponsor used 70). Also the sponsor did not include control data in their summaries of subgroup results while this reviewer included placebo for these 5 trials. The results, summarized below for LDL-C and TG for the atorvastatin 10 mg and 80 mg doses[1] and placebo, show consistent responses across all the subgroups.

Table 7. Endpoint Results by Age, Gender and Race

	Placebo		Atorvastatin 10 mg		Atorvastatin 80 mg	
	LDL-C	TG	LDL-C	TG	LDL-C	TG
Age						
<65	n=263	n=263	n=1024	n=1024	n=61	n=61
Baseline	194	200	193	179	186	252
% Change	-9%	-1%	-36%	-16%	-51%	-33%
≥65	n=89	n=89	n=443	n=443	n=17	n=17
Baseline	191	177	192	178	194	171
% Change	-14%	-4%	-39%	-17%	-56%	-30%
Gender						
Male	n=215	n=215	n=857	n=857	n=62	n=62
Baseline	190	191	191	179	184	257
% Change	-9%	-1%	-36%	-18%	-53%	-34%
Female	n=137	n=137	n=610	n=610	n=16	n=16
Baseline	198	200	195	178	203	151
% Change	-12%	-3%	-38%	-15%	-45%	-24%
Race						
White	n=322	n=322	n=1350	n=1350	n=76	n=76
Baseline	192	197	192	182	188	234
% Change	-10%	-2%	-37%	-17%	-52%	-33%
Non-white	n=30	n=30	n=117	n=117	n=2	n=2
Baseline	201	163	196	144	193	267
% Change	-12%	-4%	-37%	-15%	-56%	-17%

[1]These consistencies also were observed for the other doses studied.

The sponsor reported in their Integrated Summary of Safety that ALT levels were "the most consistent indicator of atorvastatin's effect on liver function". The sponsor also noted that there was a relationship between dose and changes in ALT. This relationship is examined further here through a plot of mean ALT versus time (Figure 1) and a table below of percentage of patients with above normal levels of ALT. At Weeks 4 to 16, ALT values for the 80 mg group are statistically significantly ($p < .005$) higher than the placebo values. This finding is supported by the high percentage of 80 mg patients (>40%) with values above normal (see table below Figure 1).

Mean ALT by Week on Study
Placebo-Controlled Trials

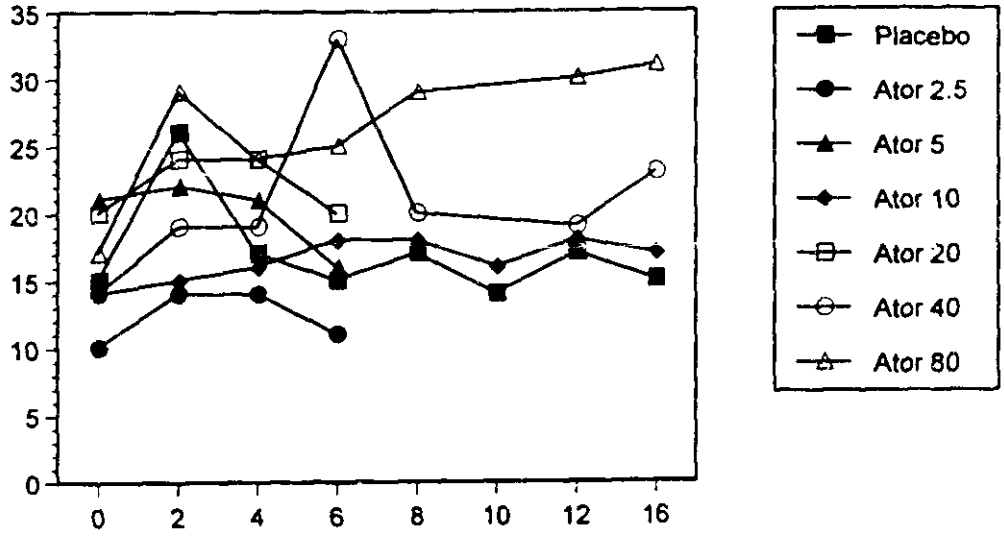

Figure 1

Percentage of Patients with ALT≥25 (ULN) by Week
Placebo-Controlled Trials

Dose[1]	0	4	6	8	10	12	16
0	10%	10%	0%	16%	8%	12%	9%
10	6%	11%	9%	18%	12%	19%	12%
40	6%	16%	45%	21%	NA	17%	28%
80	18%	37%	55%	41%	NA	43%	44%

An increase of 3 times the upper limit of normal of ALT at 2 consecutive visits was considered clinically important by the sponsor. A total of 7 patients had clinically significant ALT's while on double-blind therapy; 1 (0.5%) placebo, 1 (0.2%) on 10 mg, 1 (1%) on 40 mg and 4 (5%) on 80 mg.

The data from these 5 placebo-controlled trials clearly show that ALT increases with increasing dose.

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[1]Doses 2.5, 5 and 20 mg/day are not included here since there was no data for those doses after Week 6.

II. Review of Active-controlled Clinical Trials

The sponsor conducted 4 trials (Table 8) with active control arms in hypercholesterolemic patients. The results for 08, 09 and 37 are presented in the labeling. All of these trials had a fixed dose period followed by 1 or more periods where patients' doses could be titrated based on LDL-C levels. The focus of this review is on the fixed dose period. The inclusion/exclusion criteria for these trials were similar to the ones for the placebo-controlled trials described in Section I of this review.

Table 8. Designs of Double-blind Randomized Active-controlled Trials

Study Number (Dates Conducted)	# of Centers (Locations)	Treatment Arms	Treatment Periods
981-08 (1/94-7/95)	31 (US)	Atorvastatin 10 mg QD Lovastatin 20 mg QD Placebo	6 weeks baseline 16 weeks DB
981-09 (3/94-8/95)	26 (France, Italy, Germany, Netherlands, Spain and UK)	Atorvastatin 10 mg QD Pravastatin 20 mg QD	6 weeks baseline 16 weeks DB
981-37 (4/94-9/95)	9 (Australia)	Atorvastatin 10 mg QD Simvastatin 10 mg QD	6 weeks baseline 16 weeks DB
981-57 (3/94-8/95)	12 (Germany and The Netherlands)	Atorvastatin 10 and 20 mg QD Pravastatin 20 and 40 mg QD	6 weeks baseline 8 weeks fixed dose DB

The demographics of the patients in these studies were comparable to what was seen in the placebo-controlled trials; about 60% of the patients were male, the mean age was 57 years (range of 18 to 80) with about 30% 65 or older and more than 95% were Caucasian. The treatment groups within each study were balanced with respect to demographics.

The number of patients randomized in each of the studies is shown in Table 9 below. The randomization was 3 atorvastatin to 1 active control in all these trials to provide additional safety data for atorvastatin. Less than 10% of the patients in each group discontinued the study; about half of the dropouts discontinued treatment due to an adverse event.

Table 9. Number of Randomized Patients (Number of Dropouts)
Double-blind Randomized Active-controlled Trials

	Active Control	Atorvastatin
981-08	191 (15)	708 (50)
981-09	78 (3)	227 (10)
981-37	45 (0)	132 (2)
981-57[1]	20 mg 27 (4) 40 mg 45 (4)	10 mg 96 (3) 20 mg 128 (10)

[1] Patient numbers are for the first 8 weeks of the study; the fixed dose period.

The efficacy results of TC, LDL-C, Apo B and TG in each study (Table 10) show a statistically significantly larger decrease for atorvastatin 10 mg versus the active control. Confidence intervals[1] of the treatment difference favor atorvastatin by as much as 15% (LDL-C and TG) and as little as 1% (TG). No significant treatment differences were observed for HDL-C.

Table 10. Efficacy Results at Endpoint (LOCF)
Double-blind Randomized Active-controlled Trials

Study Treatment	Total- C	LDL-C	Apo B	TG	HDL-C	non-HDL-C /HDL-C
981-08						
Atorvastatin 10						
Baseline	276.6	192.0	177.2	179.0	48.8	4.94
% Change	-27%	-37%	-28%	-16%	+7%	-37%
Lovastatin 20						
Baseline	273.2	188.0	176.9	185.5	48.0	4.97
% Change	-19%	-27%	-20%	-6%	+7%	-28%
95% CI on Diff [2]	-9.2, -6.4	-10.7, -7.1	-10.0, -6.6	-15.2, -7.1	-1.7, 2.0	-11.2, -7.1
981-09						
Atorvastatin 10						
Baseline	277.1	194.6	151.0	146.5	53.2	4.5
% Change	-25%	-35%	-27%	-16%	+6%	-36%
Pravastatin 20						
Baseline	277.6	196.1	154.2	159.4	49.6	4.8
% Change	-17%	-24%	-17%	-10%	+8%	-28%
95% CI on Diff[2]	-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
981-37						
Atorvastatin 10						
Baseline	293.3	213.5	184.5	184.9	42.4	6.3
% Change	-29%	-37%	-33%	-22%	+7%	-39%
Simvastatin 10						
Baseline	284.1	208.4	187.5	180.4	40.1	6.3
% Change	-23%	-31%	-29%	-14%	+8%	-33%
95% CI on Diff[2]	-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9
981-57						
Atorvastatin 10			Not			
Baseline	259.6	178.1	measured at	170.3	49.3	4.7
% Change	-26%	-36%	Week 8.	-14%	+7%	-37%
Atorvastatin 20						
Baseline	296.2	215.8		151.3	50.0	5.3
% Change	-32%	-42%		-18%	+6%	-42%
Pravastatin 20						
Baseline	256.7	176.2		160.6	48.3	4.6
% Change	-16%	-23%		-4%	+2%	-17%
Pravastatin 40						
Baseline	293.7	214.0		146.8	50.4	5.1
% Change	-23%	-32%		-13%	+11%	-36%

[1] The sponsor only provided confidence intervals for Studies 8, 9 and 37; those studies whose results were presented in the proposed labeling.

[2] A negative value favors atorvastatin.

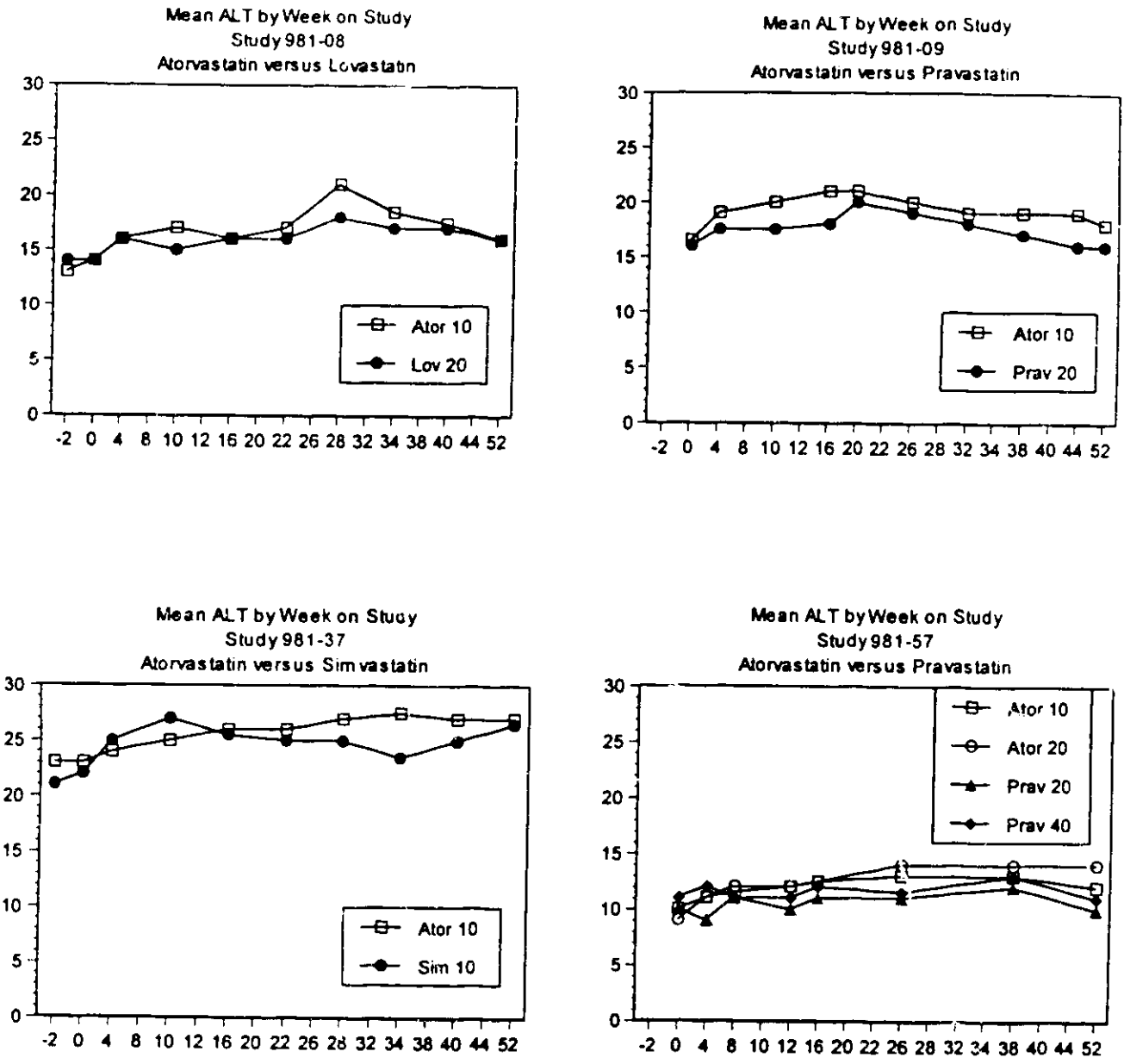

Figure 2

The mean ALT values plotted above show no significant differences between the atorvastatin groups and the active controls; however, it can be seen that, in general, the values for atorvastatin are higher. There were 5 patients who had values of ALT greater than 3xULN at 2 consecutive visits; 3 patients were on 10 mg atorvastatin.

III. Review of trials in patients with homozygous familial hypercholesteremia

Two studies were conducted by the sponsor to assess the safety and efficacy of atorvastatin 80 mg in patients with homozygous familial hypercholesterolemia; Studies 981-54 and 981-80. For Study 981-80 (an ongoing compassionate-use study), a full study report was not provided. Both studies are open label studies of atorvastatin so only descriptive statistics were presented by the sponsor.

Table 11. Designs of Trials in Patients with Homozygous Hypercholesterolemia

Study Number (Dates Conducted)	# of Centers (Locations)	Treatment Arms	Treatment Periods
981-54 (8/94-10/95)	1 (South Africa)	Atorvastatin 80 mg QD	8 weeks placebo 8 weeks open label
981-80 Compassionate-use study (4/95-present)	9 (Worldwide)	Atorvastatin 80 mg QD	4 weeks Ator 40 mg 4 weeks Ator 80 mg

The results of 37 patients in these 2 studies were presented in the NDA submission. All 8 patients in 981-54 were also studied under 981-80; they are included in the total of 29 patients for 981-80.

Table 12. Number of Patients[1]
Trials in Patients with Homozygous Hypercholesterolemia

Study Number	Atorvastatin
981-54	8
981-80 Compassionate-use study	29[2]

Table 13 on the following page gives the results by patient for both studies. In Study 981-54, all 8 patients showed a decrease of greater than 10% for LDL-C[3] (ranging from 18% to 48%, mean decrease of 31%). In Study 981-80, 25 (including the 8 patients from 981-54) of 29 patients showed a decrease in LDL-C ranging from 7% to 53% (mean decrease of 20%; 4 patients were non-responders). There were no differences in response noted between patients on plasmapheresis and patients not on plasmapheresis. The total cholesterol results paralleled the LDL-C results.

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[1]There were no dropouts in these studies.

[2]Included here are 5 children who did not take a maximum dose of 80 mg; all 5 started at a dose of 10 mg and were titrated to a maximum dose of 20, 30 or 60.

[3]The primary efficacy measure in this study was percentage of patients showing a 10% or greater change from baseline in LDL-C.

Table 13. Endpoint Results for Patients with Homozygous Hypercholesterolemia

Patient ID	Baseline LDL	LDL % Change	TC % Change	Pheresis?	Receptor Negative?	ALT Baseline/Endpoint
Study 981-54						
1						
2						
3						
4						
5						
6						
7						
8						
Study 981-80[1]						

Six of the 8 patients in Study 981-54 showed an increase at endpoint in ALT while on medication; Patient # 6 had a value at endpoint of nearly twice the upper limit of normal (ULN). Laboratory data was not provided for Study 981-80.

[1]Excerpted from Appendix B1 of the study report. The number in parentheses refers to the patient's ID number in Study 981-54.

IV. Review of clinical trials using crystalline formulation of atorvastatin

All the clinical studies described above used the amorphous formulation of atorvastatin. The marketed form of atorvastatin will be a crystalline formulation. The crystalline formulation was studied in 2 trials; 981-96 and 981-77 (Table 14). Study 981-77 is an ongoing study of 339 patients for which no data has been provided in this NDA[1]; therefore only Study 981-96 will be summarized here.

Table 14. Designs of Clinical Trials Using Crystalline Formulation of Atorvastatin

Study Number (Dates Conducted)	# of Centers (Locations)	Treatment Arms	Treatment Periods
981-96 (6/95-10/95)	5 (US)	Atorvastatin (crystalline) 10, 20, 40, 60 and 80 mg QD Placebo	6 weeks placebo 6 weeks non-blind [2]
981-77 Extension of 981-56 (Ongoing - No study report provided)	(US)	Atorvastatin (crystalline) 80 mg QD Atorvastatin (amorphous) 80 mg QD	52 weeks open label

Study 981-96 was a small study with 10-13 patients in each treatment group (Table 15). There were no dropouts in this 12 week study.

Table 15. Number of Patients Randomized
Clinical Trial Using Crystalline Formulation of Atorvastatin

Study Number	Placebo	Atorvastatin
981-96	9	11 Ator 10 mg 10 Ator 20 mg 10 Ator 40 mg 13 Ator 60 mg 12 Ator 80 mg

The results for Study 981-96 are presented with the results for Study 981-04 in order to compare the results for the crystalline formulation (981-96) to the amorphous formulation (981-04). These 2 trials were similar in design and in patient demographics with the exception of gender; in 981-04, 80% of the patients were male while in 981-96, 34% were male.

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[1] At the time of this review, a safety report for this study was to be provided to FDA within approximately 2 weeks (end of October, 1996).

[2] The study was non-blinded due to a change in drug supply resulting in nonmatching placebo tablets.

The results for 981-96 (Table 16) are markedly similar to those results from 981-04 suggesting no differences in efficacy between the two formulations. A trial comparing the 2 formulations head-to-head would confirm that they are not different.

Table 16. Comparison of Crystalline (981-96) vs. Amorphous (981-04) Formulation of Atorvastatin Efficacy Results at Week 6 LOCF (Endpoint)

Study	Placebo	Ator 2.5	Ator 5	Ator 10	Ator 20	Ator 40	Ator 60	Ator 80
Total-C								
981-96								
Baseline	275.4	NA	NA	277.6	274.1	268.6	268.7	287.2
% Change	+3%			-29%	-32%	-36%	-40%	-46%
981-04								
Baseline	267.1	262.6	267.1	281.8	278.2	271.0	NA	267.6
% Change	+5%	-17%	-22%	-31%	-35%	-38%		-46%
LDL-C								
981-96								
Baseline	190.9	NA	NA	192.3	188.4	185.2	188.5	196.5
% Change	+1%			-37%	-42%	-50%	-51%	-59%
981-04								
Baseline	184.7	182.8	185.6	196.2	196.1	185.6	NA	189.7
% Change	+7%	-25%	-30%	-41%	-45%	-50%		-61%
Apo B								
981-96								
Baseline	185.4	NA	NA	179.5	173.9	166.6	170.2	177.3
% Change	0%			-30%	-34%	-42%	-42%	-49%
981-04								
Baseline	165.7	162.8	164.5	178.2	176.4	157.5	NA	165.7
% Change	+6%	-19%	-23%	-35%	-41%	-41%		-51%
TG								
981-96								
Baseline	184.9	NA	NA	211.5	183.0	142.5	164.0	178.9
% Change	+24%			-30%	-24%	-29%	-35%	-45%
981-04								
Baseline	170.3	154.1	179.9	192.1	210.1	171.3	NA	158.2
% Change	+0.1%	-9%	-25%	-13%	-32%	-25%		-26%

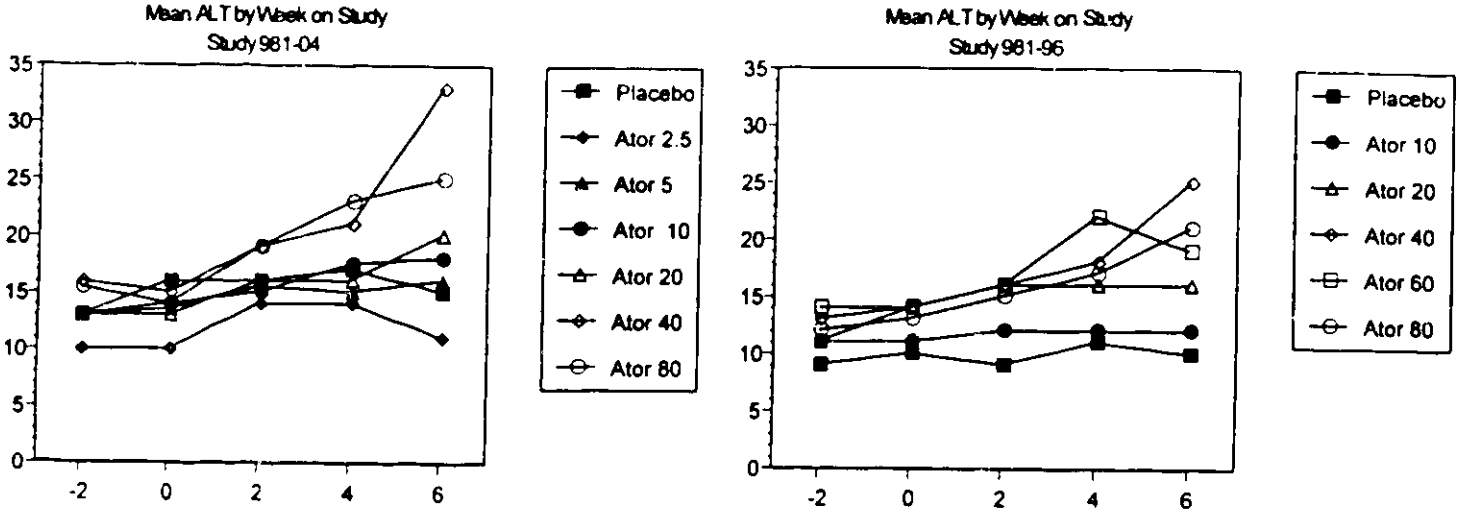

Figure 3

Percentage of Patients with ALT≥25 (ULN)
Studies 981-04 and 981-96

Dose	Week 4		Week 6	
	Study S81-04	Study 981-96	Study 981-04	Study 981-96
Placebo	8%	0%	0%	0%
Ator 10 mg	9%	0%	8%	0%
Ator 20 mg	20%	10%	25%	10%
Ator 40 mg	25%	10%	53%	40%
Ator 80 mg	46%	8%	55%	25%

Figure 3 and the table below it show that ALT increases with increasing dose. The differences between the two formulations (amorphous:981-04 and crystalline:981-96) were not considered clinically important partially due to the small number of patients in each group.

Only 1 patient had an ALT 3xULN. This patient had an ALT of 132 at Week 6 while on atorvastatin 40 mg in Study 981-04.

V. Reviewer's Comments and Labeling Recommendations

Comments:

1. The efficacy results clearly show that atorvastatin significantly reduces TC, LDL-C, Apo-B and TG compared to placebo at all the doses tested (2.5 mg/day to 80 mg/day). The full response is usually observed after 4 weeks on therapy and maintained henceforth.

2. For TC, LDL-C, and Apo B, the efficacy results show an increased response with increasing doses of atorvastatin. For TG, a dose response relationship was not evident in all the studies.

3. The rationale for the dose choices for the active controls was not given by the sponsor. It appears that doses of 2.5 and 5 would be comparable to the starting doses of the active controls (compare Tables 3-6 to Table 10) and that the sponsor has chosen a larger starting dose (10 mg) in order to show superiority over competitors. Also, note that the pravastatin 40 mg dose produces results comparable to atorvastatin 10 mg in Study 981-57. It seems to this reviewer that the utility of the active-controlled trials is limited by the small number of doses studied.

4. Very limited efficacy and safety data exists on the marketed formulation (crystalline) at the time of this review (65 patients in Study 981-96).

5. The sponsor concluded that changes in ALT were dose related. This reviewer confirmed the dose relationship by looking at changes over time (see Figures 1-3).

6. Patients with homozygous hypercholesterolemia on 80 mg of atorvastatin had a mean response of about 20%. Of 29 patients treated, 4 had no decrease in LDL. Percent decrease in LDL ranged from 7% to 53% for responders.

Labeling Recommendations:

1. Study 981-04 results are reported in the labeling. It should be noted that this study is a small study of 81 patients (10-13 patients in each treatment group) and the magnitude of the results are greater than what was observed in the other placebo-controlled studies including 981-96 (the crystalline study) therefore it may not fairly represent the expected responses. I would recommend that the results for Studies 981-04, 981-08, 981-10, 981-25 and 981-96 combined be presented as shown below. (It is reasonable to combine these studies due to the similarity of designs and results.)

Mean % Change from Baseline at Endpoint
Studies 981-04, 981-08, 981-10, 981-25 and 981-96 Combined

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	347	-7%	-10%	-7%	-1[illegible]%	+3%	-11%
10	1476	-27%	-37%	-29%	-17%	+7%	-38%
20	20	-33%	-43%	-36%	-28%	+10%	-42%
40	77	-34%	-47%	-39%	-23%	+9%	-46%
60	13	-40%	-51%	-41%	-35%	+3%	-50%
80	78	-42%	-55%	-46%	-33%	+7%	-53%

2. The proposed labeling includes tables of comparisons of atorvastatin to lovastatin, pravastatin and simvastatin. This reviewer recommends that these tables be excluded from the labeling because the comparisons may be unfair due to the limited number of doses compared (see Comment #3 above). However, if the medical division decides to include these results, then the confidence intervals for the treatment differences should be added to the tables.

3. The Warnings section of the labeling which discusses changes in serum transaminases does not mention the dose response relationship. The proposed labeling states that "Persistent increases in serum transaminases >3xULN occurred in <1% of patients who received atorvastatin". This is clearly true with all doses combined since the majority of patients in this NDA took 10 mg/day however the incidence is higher for the higher doses, particularly 80 mg/day. In the placebo-controlled trials, 5% of the 80 mg patients had ALT's>3xULN at a minimum of 2 consecutive visits. (The sponsor reports in the ISS that 3.4% of all patients taking 80 mg had ALT>3xULN). There is evidence that monitoring the liver enzymes is warranted particularly at the higher doses.

Joy D. Mele, M.S.
Mathematical Statistician

Concur: Dr. Nevius 10/24/96

Mr. Marticello

cc:
Orig. NDA 20-702
HFD-510
HFD-510/DOrloff, GTroendle, and SSobel
HFD-510/JRhee, EGalliers
HFD-715/ENevius, DMarticello, Chron
HFD-715/JMele

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Parke-Davis
Ann Arbor, MI

Submission: June 17, 1996

PHARMACOLOGY REVIEW OF NDA

DRUG: **Atorvastatin, Lipitor ™, CI-981** = open acid form (PD 130694 = lactone form)
CATEGORY: Lipid lowering (HMG CoA reductase inhibitor; synthetic, chiral)

RELATED NDAs: Lovastatin (19-643), Simvastatin (19-766), Pravastatin (19-898), Fluvastatin (20-261)

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Ronald W. Steigerwalt 10/31/96

cc: NDA Arch; HFD-510
HFD-510/Steigerwalt/Barbehenn
Atorvast.nda

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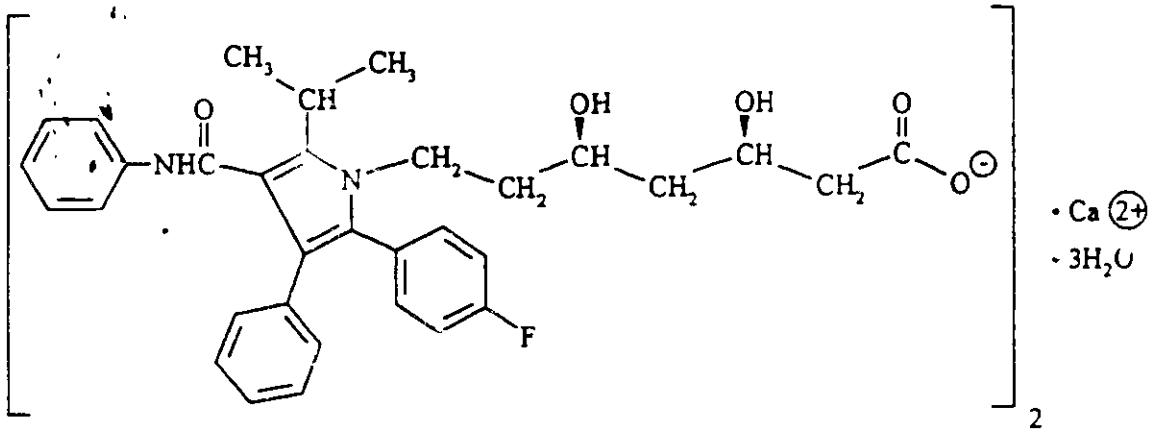

Atorvastatin

PREVIOUS REVIEWS:

December 14, 1990

2-wk rat diet (0,20,70,250 mkd)	745-01622
13-wk rat diet (0,10,30,100,200)	745-01635
2-wk dog (capsule) 0,20,80,150 mkd	745-01591
13-wk dog (capsule) 0,10,40,80 mkd	745-01594
Ames test	745-01551
Histopath effects in rats	745-01527
Peroxisome proliferation	745-01675

April 19, 1991

Dose range-finding in pregnant rabbits gavage (0,2,10,25,50,75 mkd)	745-01769

November 6, 1991

Protocols for 1-yr rat and 2-yr dog

November 15, 1991

TK rats gavage or diet 2 weeks	764-01469
Mouse micronucleus	745-01852
CHO	745-01866
Exploratory RF pregnant rats	745-01710
Teratology in rats gavage (0,10,100,300 mkd)	745-01879
Teratology in rabbits gavage (0,10,50,100 mkd)	745-01880
Histopath dog (13-week study; 0,10,40,80 mkd)	745-01874

March 25, 1992

Reply to letter of 11/19/91 re change to n mouse, dog, human

March 31, 1992

Dose-ranging dog + drug levels	250-01629

June 9, 1992

Sleep/wake cycle in rats	740-02890
Ultrastructural path of rat liver	745-01919
2-week range-finding in mice diet (0,20,100,500,700,900 mkd)	745-01932
Fertility in rats diet (0,10,50,100 mkd)	745-01980

September 4, 1992

Comments on Phase III requirements

September 16, 1992

14C distribution in male rats after 21 days	764-01869

March 8, 1993

2-wk range-finding mice gavage (0,10,50,200,400 mkd)	
Cytotoxicity of degradation product	
Oral TK dogs (10,40,120 mkd)	
Stability of drug in diet, to light	

March 8, 1993

13-week rat gavage (0,5,20,70,125 mkd)	745-02063

July 2, 1993

TK rats	764-01913
TK mice	764-02060
14C in rat brain	764-01932
Metabolic profiles	92-094 and 92-087
Interspecies comparison	764-01880

September 3, 1993

13-wk range-finding in mice gavage (0,100,200,400 mkd)	745-12114

April 7, 1994

PK in mice	764-01983; 764-02039
PK in dogs	764-02036

May 12, 1995

Single dose iv in mice (0.4,2,4 mkd)	745-02317
Single dose iv in dogs (0,0.4,2,4 mkd	745-02324
Single dose iv in rats (0,0.4,2,4 mkd)	745-02322
2-week iv in rats (0.0.4, 2,4 mkd)	745-02337
2-week iv in dogs (0,0.4,2,4 mkd)	745-02335

ADME

RR 764-02585: The amorphous form was bound to the plasma proteins (95-98% in mouse, rat, dog, human).

RR 764-01446: 14C drug was present in rat kidney and liver (up to 168 hours postdose) and **adrenal and Harder's gland** (up to 48 hours postdose) after a single oral dose of 28 mg/kg (amorphous form).

BRAIN LEVELS: RAT (RR 764-01932, part of 764-01869) (amorphous form)
Male rats were dosed with 10 mg/kg/day (10 uCi/day) for 21 days, two rats/time period were killed out to 14 days, the carcasses frozen at -80, and prepared for whole body sectioning. After sectioning was complete, the carcasses were stored at -20 until removal of remaining brain tissue; samples (15 to 116 mg) were oxidized and counted. Any measurement less than 2x background was considered 0.00 ug. **Four rats had measurable radioactivity at one timepoint postdose: 24 (two), 48 (one), and 336 hours (one).** To obtain definitive data, however, a higher dose and larger samples would need to be employed with the brains stored at -80°. Calculations need to be done to estimate the minimum level of detectable using this dose and radioactivity.

BRAIN LEVELS: DOG 14C (RR 764-01948) (1993) (Amorphous form)
One male and one female were given 7 mg/kg tid for 10 days. These unlabeled doses were followed 4 hours later with a radiolabeled dose of 3 uCi/mg and plasma and brains removed and frozen at -80.

	Plasma (dpms/ml)	**Brain (dpms/g) (solubilization)**	**Brain (dpms/g) (oxidation)**
Female dog	2,700	150	BLQ
Male dog	1,200	BLQ	BLQ
Limit of quantitation	60	77	370

BLQ= below level of quantitation

13-WEEK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN DOGS
PK IN DOGS (MALE AND FEMALE): **WEEKS 6 OR 7**

	Cmax (ug/ml)		**AUC 0-24 (ug hr/ml)**		**t1/2 (hr)**	
DOSE (mkd)	**Amorphous**	**Crystalline**	**Amorphous**	**Crystalline**	**Am**	**Cry**
10	75 ± 23	140 ± 40	460± 100	480± 120	7± 5	5± 2
40	410 ± 50	1,900± 1,800	1,300± 500	8,200± 9,800	8± 4	5± 1
120	880± 920	9,000± 11,000	4,100± 3,000	63,000± 69,000	5± 1	5± 2

There was only 1/6 dogs alive at 120 mkd (crystalline) at week 13 and variability was so great that no conclusions can be drawn as to their response over time.

13-WEEK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN DOGS
RANGE OF VALUES (WEEKS 6 OR 7)

	Cmax (ug/ml)		**AUC 0-24 (ug hr/ml)**		**t1/2 (hr)**	
DOSE (mkd)	Amorphous	Crystalline	Amorphous	Crystalline	Am.	Cry.
10	60-100	70-170	300-600	370-640	5-15	2-7
40	70-1,500	360-5,200	600-2000	3,300-28,000	5-14	3-6
120	140-2,500	4000-25,000	1000-8000	17,000 to 165,000	4-7	4-8

PK RATIO (crystalline to amorphous) in dogs

DOSE	RATIO Cmax	RATIO AUC
10 mkd	2	1
40 mkd	5	6
120 mkd	10	15

PLASMA DRUG LEVELS IN MALE DOGS (2-year study):

	Week 24		**Week 50**		**Week 76**		**Week 102**	
DOSE	Cmax ng/ml	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC
10 mkd	**94**	500	**96**	470	**90**	480	**60**	450
40 mkd	**710**	2,800	**150**	320	**490**	1,500	**370**	1,300
120 mkd	**2,600**	11,000	**720**	3,000	**80**	400	**820**	5,400

PLASMA DRUG LEVELS IN FEMALE DOGS (2-year study):

	Week 24		**Week 50**		**Week 76**		**Week 102**	
DOSE	Cmax	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC
10 mkd	**120**	530	**120**	470	**130**	480	**95**	560
40 mkd	**720**	2,600	**460**	1,500	**370**	1,200	**450**	1,800
120 mkd	**1,100**	4,500	**780**	4,300	**990**	3,700	**3,400**	12,000

RR 764-02533: ADME IN DOGS USING 14C DRUG (vol 1.75)
(Amorphous form lot XH030193) Sept. 1995
Three males and 3 females were given a **single 10 mg/kg oral dose of 14C atorvastatin or PD 130694 in 0.5% methyl cellulose in 2-way crossover** (with blood collected up to 192 hours). There was a 1 month wash-out between treatments.

Fecal excretion of atorvastatin cpm was 96% (one dog was 42%; rest were 100%)
Fecal excretion of PD 130694 cpm was 90% (one dog was 56%; rest were 90-100%)

Urinary excretion of atorvastatin cpm was 0.32% (range was 0.2-0.5%)
Urinary excretion of PD 130694 cpm was 0.51% (range was 0.3-0.8%)

Peak radioactivity atorvastatin: 4 hours postdose with 500 ng eq/ml plasma
Peak radioactivity PD 130694: 1 hours postdose with 430 ng eq/ml plasma

Peak enzyme inhibition atorvastatin: 0.25 hours postdose with 160 ng eq/ml
Peak enzyme inhibition PD 130694: 1 hours postdose with 190 ng eq/ml plasma

Comparison Enzyme Activity and Radioactivity in Dogs*

	HMG CoA reductase inhibition AUC (0-∞)	Radioactivity AUC (0-∞)	HMG/Radioactivity Ratio (%)
Atorvastatin (acid)	364	24,000	2%
PD 130594 (lactone)	510	6,100	8%

(*a single dose of 10 mg/kg; amorphous form)

This indicates that there are many metabolites that are not detected with the enzyme inhibition assay. Here, only 2% of atorvastatin (open acid) was detectable by enzyme inhibition (98% was present as inactive metabolites) only 8% atorvastatin ( ).

ADME (DOGS) Amorphous form

RR 745-01873 (Rising dose range-finding study in dogs; 2 males & 2 females)

WEEK	DOSE	Cmax (ng/ml)	AUC 0-8 hours (ng hr/ml)
1	80	300 (160-640)	2,400
2	80	640	3,500
4	120	2,200	7,700
5	140	960	3,600
6	160	1,600	6,400
7	180	530	4,200
8	200	2,000	9,000
9	220	700	7,700 (6,100-9,200)
10	240	4,000	26,000 (19,000-35,000)
11	280	2,400	11,000 (6,000-16,000)

ADME (RATS)
(AMORPHOUS vs CRYSTALLINE)
MALES, RATS 13-WEEK TOXICITY STUDY

	Cmax (ng/ml)		**AUC 0-24 (ng hr/ml)**		**t1/2 (hours)**	
	crystal	amorph	crystal	amorph	crystal	amorph
10	110	98	740	420	3	4
30	430	320	2,600	1,200	4	6
100	6,700	3,100	21,000	13,000	3	4

PK (FEMALE RATS) 13-WEEK TOXICITY STUDY

	Cmax (ng/ml)		**AUC** 0-24 (ng hr/ml)		**t1/2** (hours)	
	crystal	amorph	crystal	amorph	crystal	amorph
10	130	48	330	370	12	16
30	310	140	790	640	4	8
100	2,300	2,500	12,000	9,500	5	6

Tmax: 1 hour for all

RATIO Crystalline:Amorphous (in rats)

Cmax		**AUC**		**t1/2**		**Dose**
Male	Female	Male	Female	Male	Female	(mg/kg)
1.1	2.7	1.8	0.9	0.8	0.7	10
1.3	2.2	1.3	1.3	0.7	0.4	30
2.2	0.92	1.6	1.2	0.9	0.7	100

Tmax: 1 hour for all

PHARMACOKINETICS IN WISTAR RATS

RR764-02219. Parke-Davis

TREATMENT: Groups of 7 rats/s/group (~9 weeks old) were given either single or 14 daily doses of **10, 30, or 100 mg/kg orally** by gavage in 0.5% methylcellulose. Blood was collected pre-dose and at times up to 216 hours postdose (single dose) or 72 hours postdose (14 doses).

RESULTS: There was "high interanimal variability" in all dose groups with percent relative standard deviations of 35 to 200%.

PHARMACOKINETICS IN WISTAR RATS (amorphous form)

DAY 1

DOSE	Cmax (ng/ml)		tmax (hour)		AUC (ng h/ml)	
	Male	Female	Male	Female	Male	Female
10 mkd	340	160	2	1	1,200	750
30 mkd	800	410	1	0.5	2,200	1,200
100 mkd	3,900	2,400	1	1	13,000	5,900

DAY 14

DOSE	Cmax (ng/ml)		tmax (hour)		AUC (ng h/ml)	
	Male	Female	Male	Female	Male	Female
10 mkd	200	150	1	0.5	640	370
30 mkd	730	750	1	2	2,300	3,100
100 mkd	1,800	760	2	3	8,600	4,700

RAT CARCINOGENICITY STUDY (amorphous form)
PLASMA CONCENTRATIONS IN RATS ONE HOUR POSTDOSE (6/g) DW 52

DOSE (mg/kg/day)	**MALES**	**FEMALES**
10	130 ± 110	160 ± 73
30	510 ± 240	230 ± 200
100	1,400 ± 830	1,500 ± 1,000

PREGNANT FEMALE RATS (RR 745-02283; amorphous form)
PLASMA PK (Lactation day 8)

Treatment group	**Cmax (ng/ml)**	**AUC (ng h/ml)**	**t1/2 (h)**	**tmax (h)**
20 mkd	104 ± 60*	803 ± 310	11± 7	2
100 mkd	1050 ± 900	6,100 ± 5,100	5 ± 4	3
225 mkd	5800 ± 5700	22,000 ± 17,000	3 ± 1	2

*Mean ± %RSD

FEMALE RATS (RR 745-02295; amorphous form)
PLASMA PK (pre-mating day 14; 5/g)

	Cmax (ng/ml)	**$AUC_{(0-24)}$ (ng eq h/ml)**	**tmax (h)**
20 mkd	81 ± 28	480 ± 95	1 ± 0
100 mkd	2030 ± 1,100	9,800 ± 5,500	2 ± 3
225 mkd	7030 ±3,700	56,000 ± 46,000	5 ± 4

Mean±S.D.

MALE RATS (RR745-02298; amorphous form); **PLASMA PK** (15 weeks treatment; 5/g)

	20 mkd	**100 mkd**	**175 mkd**
Cmax (ng eq/ml)	110 ± 30*	1,300 ± 620	1,800 ± 1,000
tmax (hr)	5 ± 5	2 ± 3	4 ± 4
AUC_{0-24} (ng eq h/ml)	930 ± 350	7,200 ± 4,100	15,000 ± 9,700

*Mean±SD

RAT CARCINOGENICITY STUDY (amorphous form)
PLASMA CONCENTRATIONS IN RATS ONE HOUR POSTDOSE (6/g) DW 52

DOSE (mg/kg/day)	**MALES**	**FEMALES**
10	130 ± 110	160 ± 73
30	510 ± 240	230 ± 200
100	1,400 ± 830	1,500 ± 1,000

PREGNANT FEMALE RATS (RR 745-02283; amorphous form)
PLASMA PK (Lactation day 8)

Treatment group	**Cmax (ng/ml)**	**AUC (ng h/ml)**	**t1/2 (h)**	**tmax (h)**
20 mkd	104 ± 60*	803 ± 310	11± 7	2
100 mkd	1050 ± 900	6,100 ± 5,100	5 ± 4	3
225 mkd	5800 ± 5700	22,000 ± 17,000	3 ± 1	2

*Mean ± %RSD

FEMALE RATS (RR 745-02295; amorphous form)
PLASMA PK (pre-mating day 14; 5/g)

	Cmax (ng/ml)	**$AUC_{(0-24)}$ (ng eq h/ml)**	**tmax (h)**
20 mkd	81 ± 28	480 ± 95	1 ± 0
100 mkd	2030 ± 1,100	9,800 ± 5,500	2 ± 3
225 mkd	7030 ±3,700	56,000 ± 46,000	5 ± 4

Mean±S.D.

MALE RATS (RR745-02298; amorphous form); **PLASMA PK** (15 weeks treatment; 5/g)

	20 mkd	**100 mkd**	**175 mkd**
Cmax (ng eq/ml)	110 ± 30*	1,300 ± 620	1,800 ± 1,000
tmax (hr)	5 ± 5	2 ± 3	4 ± 4
AUC_{0-24} (ng eq h/ml)	930 ± 350	7,200 ± 4,100	15,000 ± 9,700

*Mean±SD

RAT PLASMA DRUG CONCENTRATIONS (drug week 26 of 1-yr study)
RR 764-02288

DOSE	**MALE** (ng/ml)		**FEMALE** (ng/ml)	
	2 Hour	4 Hour	2 Hour	4 Hour
5 mkd	31 ± 17	23 ± 22	6 ± 3	2.9 ± 1
70 mkd	540 ± 270	110 ± 44	130 ± 30	41 ± 26
125 mkd	870 ± 530	220 ± 86	93 ± 56	49 ± 21

ADME (MICE)
PK (MALE MICE) 13-WEEK COMPARISON STUDY (Crystalline vs Amorphous)
RR 745-02436

	Cmax (ng/ml)		**AUC (0-24 hr)** (ng hr/ml)		**t1/2** (hours)	
	crysta	**amorph**	**crystal**	**amorp**	**crystal**	**amorph**
10	190	440	520	760	4	4
30	630	1,100	1,200	1,800	4	4
100	1,600	7,100	4,900	9,300	5	3

PK (FEMALE MICE) 13-WEEK COMPARISON STUDY (Crystalline vs Amorphous)
RR 745-02436

	Cmax (ng/ml)		**AUC (0-24 hr)** (ng hr/ml)		**t1/2** (hours)	
	crysta	**amorph**	**crystal**	**amorp**	**crystal**	**amorph**
10	820	9,000	1,400	9,300	2	3
30	3,200	4,600	6,000	5,500	0.6	3
100	3,100	16,000	6,500	19,000	1	3

RATIO Crystalline/Amorphous in mice (13 week study)

Cmax (ng/ml)		AUC (0-24 hr)		t1/2 (h)		Dose (mg/kg)
Male	Female	Male	Female	Male	Female	
0.42	0.09	0.67	0.14	1.0	0.63	100
0.56	0.71	0.63	1.0	1.1	1.7	200
0.23	0.20	0.53	0.33	1.7	0.77	400

MOUSE CARCINOGENICITY STUDY (amorphous form)
PLASMA CONCENTRATIONS IN MICE 1/2 HOUR POSTDOSE (10/g) DW 100

DOSE (mg/kg/day)	MALES	FEMALES
Untreated control	0.9*	1.3
Vehicle control	2.8	0.8
100 mkd	520	1,400
200 mkd	470	2,600
400 mkd	3,700	3,800

PK HUMAN STUDIES
RR 744-00115: A.M. vs P.M (40 mg for 15 days) (Amorphous form)

Parameter	Morning (n=15)	Evening (N=15)	Difference (AM/PM)
Cmax (ng/ml)	**95** (44)*	**66** (52)	-31%
AUC $_{0\text{-}24}$ (ng hr/ml)	**650** (37)	**460** (38)	-29%
tmax (hr)	1.9 (63)	2.9 (78)	+57%

*%RSD (relative standard deviation)

HUMAN PK

RR 744-00256 Single 40 mg dose Crystalline vs Amorphous (A.M. n=36)

Parameter	**Amorphous**	**Crystalline-1**	**Crystalline-2**
Cmax (ng/ml)	**21** (54)*	**35** (86)	**32** (65)
$AUC_{0-\infty}$ (ng hr/ml)	**148** (49)	**164** (58)	**166** (58)
tmax (hr)	**1.8** (92)	**1.0** (67)	**0.94** (79)

*%RSD (relative standard deviation)

Crystalline-1 (non-market image; Morris Plains manuf.)
Crystalline-2 (market-image; Lititz manuf.)

RR 744-00247: Crystalline doses for 8 days (crossover; n=16; **A.M. dosing**)

	10 mg		**20 mg**		**40 mg**		**80 mg**	
Parameter	EIA	Act*	EIA	Act.	EIA	Act.	EIA	Act.
Cmax (ng/ml)	10	6.5	23	15	**48**	**27**	**140**	94
AUC_{0-24} (ng hr/ml)	120	79	250	170	**370**	**220**	**990**	720
tmax (hr)	3.5	4	1.7	4	**1.4**	**3**	1.8	2
t1/2 (hr)	30	33	23	31	**18**	**32**	**20**	24

Dog mortality at AUC 8,200 ng eq h/ml = 8x human AUC of 990 ng eq/ml.
Cmax 1,900 ng eq/ml =14x human Cmax of 140 ng eq/ml.

RR 744-00208: 10 mg crystalline dose for 1 day (A.M. dosing)

	Crystalline	Amorphous
Cmax (ng/ml)	7.1 (46)	5.7 (41)
AUC_{0-24} (ng hr/ml)	81 (49)	72 (41)

HUMAN PK (FOOD EFFECT).

Amorphous form (10 mg/day for 15 days)

Parameter	With Meals	After Meals	Difference (%)
Cmax (ng eq/ml)	3.1	4.1	-25
tmax (hours)	6.0	3.6	67
$AUC_{(0-24)}$	51	65	-22

Crystalline form (10 mg crystalline for 15 days in the evening)

Parameter	With Meals	After Meals	Difference (%)
Cmax (ng eq/ml)	5.3	7.1	-25
tmax (hours)	4.4	3.4	30
$AUC_{(0-24)}$	84	92	-9

HUMAN: People given a single dose of **10 mg oral**

Amorphous form

Cmax (ng/ml)	tmax (hours)	AUC 0-∞ (ng h/ml)	t1/2 (hours)
5.5	3.8	120	36

HUMAN: People given a single dose of **5 mg iv**

Amorphous form

Cmax (ng/ml)	tmax (hours)	AUC 0-∞ (ng h/ml)	t1/2 (hours)
67	1.7	190	21

Bioavailability (human; amorphous form): 31% of single 10 mg dose

IN VITRO HUMAN MICROSOMAL METABOLISM OF CI-981
RR 764402313. January to July 1994. Parke-Davis.

"There were no qualitative differences in the [14C]CI-981 metabolic profiles generated by rat, dog, and human hepatic microsomal preparations" but no identifications were made. Now, two metabolites have been identified that were produced both by human liver (tissue from 5 males) and human intestinal microsomes (tissue from one female).

STABILITY OF CI-981 IN DIET ADMIXTURES
RR 730-01816. 1992. Parke-Davis
METHOD #1: Lot XH360990 was used to prepare diet admixtures of 0.05 and 5.0 mg/g diet and assayed by periodically over 28 days for CI-981 (open acid form), PD 130694 and unknown A.

Results: Lot XH330789 had previously been found to be stable in the diet for up to 21 days but admixtures of XH 360990 were stable "for less than 1 week in terms of CI-981". There was a 30% loss by 28 days (0.05 mg/g) and 25% (5.0 mg/g). The accounted for 8 and 12% and unknown A was either not detectable or 2%. Different lots of Purina chow made no difference in stability.
"The rate of degradation of CI-981 and formation of the lactone and unknown A in the admixtures varied dramatically from lot to lot of CI-981."

STABILITY OF CI-981 IN DIET ADMIXTURES

Results:

LOT NUMBER	Area %* (original)	Area % (day 14)	Area % (day 35)
XH180489	96	93	93
XH330789	95	91	91
XH450989	96	87	86
XH711289	96	85	84
XH160490	96	85	80
XH210490	96	92	90
XH220490	95	79	74
XH360990	96	84	81
XH420990	97	81	79
XH441090	97	78	71
XH140391	97	85	82
XH170391	97	82	76
XH250691	98	92	90
XH330891	98	80	75
XH350891	98	82	78
XH461291	98	92	87

PHOTODECOMPOSITION OF CI-981 BY UV LIGHT
RR 730-01720. Issued October 1991. Parke-Davis.

Results: After 6 hours, there was no starting material detectable; there were "four prominent decomposition peaks and more than 10 lesser peaks". The proposed structures were provided.

Exposure time (hours)	% left (area)
0	98
1	90
2	76
3	53
4	29
5	1
6	not detectable

2-WEEK STUDY COMPARING THREE DIFFERENT LOTS OF DRUG IN MICE
RR 745-02237. September 1993. Parke-Davis. Amorphous form.
TREATMENT: Groups of B6C3F1 mice (10/s/g; 9-11 weeks old) were treated for 2 weeks with three different lots of drug at doses of **0, 400, 800, or 1200 mg/kg/day** in 0.5% methylcellulose (lots XH030193, XH200593, and XH080292). Histopathology was done on the liver and adrenal from all mice which survived to necropsy. Submandibular salivary glands noted to be enlarged were examined from 8 males at 400 mkd lot 80292. The stomachs from several males of each lot treated with 800 mkd or 1200 mkd were also examined.

Lot (No.)	Active Moiety (%)	Use
XH030193:	91.2%	Being used in carcinogenicity study
XH080292:	89.1%	Was used in previous studies where deaths occurred at 400 mkd
XH200593:	92.8%	To compare a lot prepared by current practice of isolating the lactone (prior to conversion to open acid, CI-981)

2-WEEK STUDY COMPARING THREE DIFFERENT LOTS OF DRUG IN MICE
RESULTS (continued)
MORTALITY

LOT NO. (% purity)	400 mkd	800 mkd	1200 mkd
XH030193 (91%)	0%	**30%**	**80%**
XH200593 (93%)	0%	**65%**	**100%**
XH080292 (89%)	**10%**	**100%**	**100%**

Lot Dose #died
089292 (400 mkd): 1 male and 1 female
030193 (800 mkd): 1 male and 5 females (1200 mkd): 6 males and 10 females
200593 (800 mkd): 3 males and 10 females

CLINCIAL SIGNS
Mice that died (all lots):
Hypoactivity and reduced skin turgor (dehydration)
Reduced or lacking feces, thin appearance, urine stain, coolness to touch
Mice that lived (lot XH080292): Reduced feces in all 10 females at 400 mkd

BODY WEIGHT GAIN:
Males (800 mkd; lot 080292): lost 5 g
Females (800 mkd; lot 080292): lost 3.5 g
Females (800 mkd; lot 200593): lost 3 g
Females (800 mkd; lot 030193): lost 0.9 g

FOOD CONSUMPTION: decreased ≥800 mkd all lots

CLINICAL CHEMISTRY (males in IU/L):

Lot No.	**ALT**	**AST**	**ALKP**	**CPK**
Dose group:	L, M, HD	L, M, HD	L, M, HD	L, M, HD
(no drug; control)	(50)	(180)	(130)	(740)
XHO30193	70, 95, 250	220, 400, 1700	150, 170, 180	700, 760, 810
XH200593*	80, 120	210, 500	150, 160	770, 200
XH080292#	110	360	180	420

*no HD left
no M or HD

2-WEEK STUDY COMPARING DIFFERENT LOTS OF DRUG IN MICE (cont.)
(0, 400, 800, 1200 mg/kg/day by gavage)

CLINICAL CHEMISTRY (females in IU/L):

Lot No.	ALT	AST	ALKP	CPK
Dose group:	LD, MD	LD, MD	LD, MD	LD, MD
(no drug; control)	(43)	(120)	(190)	(260)
XHO30193*	50, 160	110, 1000	250, 180	160, 460
XH200593#	60	130	240	30
XH080292#	90	500	220	320

*no HD left
#no M or HD left

GROSS PATHOLOGY (DYING, MORIBUND)

Lot No.	**#30193**				**#200593**				**#080292**						
Sex	**male**		**female**		**male**		**female**		**male**			**female**			
Dose	**M**	**H**	**M**	**H**	**M**	**H**	**M**	**H**	**L**	**M**	**H**	**L**	**M**	**H**
No. Mice	**2**	**6**	**5**	**10**	**3**	**10**	**10**	**10**	**1**	**10**	**10**	**1**	**10**	**10**
LIVER														
Abnormal color	0	1	1	2	0	4	2	1						
STOMACH (glandular)														
Abnormal color	1	2	0	3	1	9	3	4	0	7	7	0	4	7
Abnormal content	0	5	2	10	1	10	7	10	0	9	10	0	10	10
THYMUS (small)	1	6	4	10	3	10	10	10	0	10	10	0	10	10
SKIN (urine scald)								1	0	0	2	0	0	0

GROSS PATHOLOGY (terminal)
SUBMANDIBULAR SALIVARY GLAND: enlarged in 8/9 males at 400 mkd lot 200593

HISTOPATHOLOGY (dying/moribund) not done
HISTOPATHOLOGY (terminal) (only Liver, Stomach, and Adrenal examined)
LIVER: hypertrophy, eosinophilia, single cell necrosis, mitosis increased

13-WEEK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN DOGS (vol.1.58)
RR 250-01749. May 1995. Parke-Davis.
Lots: XH020193 (amorphous form) and XH020195 (crystalline form)

TREATMENT: Nine groups of beagle dogs (3/s/g; ~33 months of age at initial dose) were given in capsules, **0, 10, 40, or 120 mg/kg/day (amorphous**; *groups 1-4*); **10, 40, or 120 mg/kg/day (crystalline**; *groups 5-7*) or control (*group 8*) and escalating doses of 80 mkd (weeks 1-2) and 100 mkd (weeks 3-4) for *group 9*. Blood was collected weeks 6 (females) and 7 (males) predose and 1, 2, 4, 8, 12, and 24 hours postdose. In addition, blood was taken from one male and one female that died early. Samples of liver from all dogs were collected, fixed, processed, and stored but ultrastructural evaluation was not performed.

RESULTS

MORTALITY (Cause of death not provided)
Amorphous: none
Crystalline: 2/3 HD males (weeks 5 and 6)
1/3 MD female (week 8) and 3/3 HD females (weeks 3, 5, 6)

CLINICAL SIGNS: (see attached sheet)
Crystalline (dogs that died): "Diarrhea, mucoid and/or unformed feces often containing blood; emesis, reduced food consumption, hypoactivity, weight loss, emaciation, salivation, prostration, pallor or pale mucous membranes. Two males showed dysphagia and pain when opening or palpating the mouth or tongue."

BODY WEIGHT
Amorphous: No significant effects
Crystalline: No effects on dogs that lived; weight loss of ~25% occurred in dogs that died.

FOOD CONSUMPTION
Amorphous: No treatment-related effects
Crystalline: No effects on dogs that lived; reduced at 40 and 80 mkd

OPHTHALMIC EXAM: "No effects" (no data)

ECG: "No effects" (no data)

BLOOD PRESSURE: "No effects" (no data)

13-WEEK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN DOGS

HEMATOLOGY

Amorphous: no effects

Crystalline: (*Dogs that died*)

Hct, Hgb: increased or decreased

WBC: increased to 2-5x pretest due to higher neutrophil counts

Crystalline: (*Dogs that lived*)

Total leukocyte count up 2x (HD males); neutrophils up 2x

BONE MARROW (*p<0.01)

Amorphous: Proliferating erythroid: 19.6; 18.4, 19.6, 14.1*% (Males)

Crystalline (*dogs that died*):

	Died vs Control (examples of male values)
Maturing erythroid (%):	5% vs 28%
Proliferating erythroid (%):	3% vs 20%
Maturing myeloid (%):	80% vs 46%
Myleoid/erythroid ratio	10 vs 1

	MALES	FEMALES
	0 10 40 120 mkd	**0 10 40 120** mkd
Crystalline (*dogs that lived*):	N=3; 3, 3, 1	N=3; 3, 2 (+3 HD at death)
Maturing erythroid (%):	28; 23, 20, 21	24; 19, 31, 14
Proliferating erythroid (%):	20; 19, 14, 16	15; 12, 21, 8
Maturing myeloid (%):	46; 47, 53, 54	52; 59, 36, 58
Myleoid/erythroid ratio	1.0; 1.2, 1.7, 1.5	1.4; 2.0, 0.8, 2.6
Myleoid mat. index	23; 15, 12, 21	21; 34, 7.6, 38

BIOCHEMISTRY (wk 13; *p<0.01)

Amorphous:	**MALES (3/s/g)**	**FEMALES (3/s/g)**
	0 10 40 120 mkd	**0 10 40 120** mkd
ALT	32; 44, 100, 800	31; 32, 52, 160
ALKP	34; 68, 43, 660	62; 43, 57, 110
CHOLESTEROL (mM)	2.9; 2.1, 1.7, 1.3	4.7; 3.6, 2.1, 1.5
PHOSPHOLIPIDS (mM)	3.2; 2.2, 1.8, 1.5	4.7; 3.7, 2.4, 1.8*
TG (mM)		0.5; 0.6, 0.3, 0.3
CRYSTALLINE:	**n= 3 3 3 1**	**n= 3 3 2 0**
ALT	34; 43, 76, 180	31; 42, 58 no dogs @ 120 mkd
ALKP	34; 48, 63, 73	62; 77, 47 -
CHOLESTEROL	2.9; 2.5, 1.8, 1.0	4.7; 3.5, 2.4 -
PHOSPHOLIPIDS		4.7; 3.7, 2.8 -
TG		0.5; 0.5, 0.4 -

13-WEEK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN DOGS
URINALYSIS

Amorphous: No effects

Crystalline: Moderate or large amounts of blood in dogs that died
Bilirubin, urobilinogen, leukocytes, WBC, RBC seen

PATHOLOGY

ORGAN WEIGHTS (g/g brain; *p<0.01 level):

Amorphous: No effects

Crystalline:
MALES: No effects
FEMALES: (not signif at p<0.01 but clear trend)
Uterus 0.125; 0.214, 0.053 (0,10, 40 mkd)
Spleen: 0.788; 1.357, 1.990 (0, 10, 40 mkd)

GROSS (3/s/g)

Amorphous TERMINAL SACRIFICE
Large intestine: discoloration of the large intestinal mucosa (all females @ 120 mkd)
discoloration described as "red" in body of report (table says only discoloration)

GROSS

Crystalline: MORIBUND
BODY FAT: decreased
MUSCLE MASS: decreased
ADRENAL: enlarged and red discoloration
GALLBLADDER: thick wall 0, 1, 3 (L,M,HD)
STOMACH: red discoloration of mucosa and edema
LARGE INTESTINE: red discoloration
LYMPH NODES: red discoloration and enlargement
SPLEEN: small and contracted
RENAL MEDULLA: white streaking

Also:
CECUM MUCOSA, COLON MUCOSA discoloration (HD M and F)
SMALL INTESTINE: discoloration duodenum, ileum, jejunum mucosa (HD F)
LIVER discoloration (MD M)
Abnormal surface (MD F and HD M)

Crystalline: TERMINAL SACRIFICE
LARGE INTESTINE: red discoloration (congestion) in 1 female @ 10 and 40 mkd

13-WEEK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN DOGS
HISTOPATHOLOGY

Amorphous (terminal sacrifice)
GALLBLADDER: congestion (minimal/mild) in males at 120 mkd and females at ≥40 mkd
BILE DUCT: hyperplasia (minimal/mild) in males ≥40 mkd and females at 120 mkd

Crystalline (dead or moribund dogs)
ADRENAL: necrosis with congestion or hemorrhage & cholesterol clefts
GALLBLADDER: edema, congestion and/or hemorrhage, neutrophilic infiltrates
BILE DUCT: hyperplasia
LIVER: atrophy, pigmentation, vacuolation, lipidosis (Ito cell)
STOMACH: congestion
INTESTINAL TRACT: congestion (hemorrhage)
MUSCLE: degeneration in tongue, diaphragm, masseter and/or psoas muscles
LUNG: alveolar edema, hemorrhage, fibrin deposition
SPLEEN/LYMPH NODE: lymphoid depletion

Crystalline (terminal sacrifice)
PSOAS MUSCLE: degeneration at 40 mkd (1 male)

13-WEEK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN RATS (vol.1.57)
RR 745-02436. May 1995. Parke-Davis.
Lots: XH020193 (amorphous form) and XH020195 (crystalline form)
TREATMENT: Seven groups of 6-7 week old Wistar rats (14/s/g for controls and 22/s/g for treated) were given 0 (0.5% methylcellulose), or **10, 30, or 100 mg/kg/day** of either amorphous or crystalline form of drug. The first 10/s/g were for toxicology, the last 4/s/g (controls) and 12/s/g (treated) were for plasma drug analyses.

RESULTS
MORTALITY:
One control male: rales
Amorphous: one 10 mg/kg female ("gavage error") and one 100 mg/kg male (unknown)
Crystalline: one 100 mkd female ("gavage error")

13-WK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN RATS (0,10,30,100 mkd)

BIOCHEMISTRY (Amorphous)

	MALES				**FEMALES**			
Dose mkd	**0**	**10**	**30**	**100**	**0**	**10**	**30**	**100**
Ca	11.2	11.1	11.0	10.7*	11.3	11.2	11.3	10.8*
TG	54	44.8	35.5	31.2*	40.4	39.8	36.5	28.0*
AST	104	106	117	170*	93	81	99	91
ALT	48.6	63.9	70.0*	93.4*	51	44	49	63
ALKP	104	99.8	102	134*	57.8	69.3	82.5	75.2*
T.protein	6.62	6.13	6.10	6.06*	7.24	7.09	7.00	6.75
Albumin	3.50	3.30	2.84	2.83*	4.12	4.04	3.94	3.72*
Urea nitrog	14.7	15.0	12.9	12.7*	15.7	14.9	17.1	16.7

BIOCHEMISTRY (Crystalline)

	MALES				FEMALES			
	0 mkd	**10 mkd**	**30 mkd**	**100 mkd**	**0 mkd**	**10 mkd**	**30 mkd**	**100 mkd**
Ca	11.2	10.8	11.0	10.5*	11.3	11.2	11.3	10.79*
TG	54.0	43.1	51.4	28.0*	40.4	37.3	35.1	31.0*
AST	104	119	114	170*	93	95	85	91
ALT	48.6	82.2	75.5	101*	50.9	46.4	46.6	85.2
ALKP	104	105	118	133*	57.8	53.7	58.0	71.7
T.protein	6.62	6.34	6.38	5.60*	7.24	7.0	6.97	7.0
Albumin	3.50	3.42	3.45	3.10*	4.12	4.04	3.94	3.72*
Globulin	3.12	2.93	2.94*	2.50*	3.12	2.93	8	3.02
Alb/Glob.	1.13	1.17	1.19	1.25*	1.33	1.39	1.35	1.32
Sodium	148.5	147.4	147.3	145.3*	148	148	148	146
Urea nitrog	14.7	15.0	12.9	12.7*	15.7	16.0	17.0	16.6

13-WK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN RATS (0,10,30,100 mkd)
URINALYSIS
Amorphous: no signficant effects
Crystalline: no significant effects

PATHOLOGY
ORGAN WEIGHTS (% of brain weight; ***p<0.01**):

Amorphous:	**MALES**	**FEMALES**
	0; 10,30,100 mkd	0; 10,30,100 mkd
Liver:	7.20; 6.46*, 6.24*, 6.23*	3.9; 4.4, 4.8*, 5.1* (0,10,30 100 mkd)
Testis:	1.83; 1.76, 1.69, 1.70*	
Spleen:	0.46; 0.46, 0.45, 0.51*	0.31; 0.33, 0.34, 0.36
Lung:		0.72; 0.77, 0.79, 0.81*

Crystalline:	MALES	FEMALES
	0; 10,30,100 mkd	0; 10,30,100 mkd
Liver	7.2; 6.2*, 6.5*, 6.0*	3.9; 4.3, 4.6*, 4.9*
Sal.gland	0.42; 0.39*, 0.38*, 0.38*	0.27; 0.27, 0.27, 0.29
Testis:	1.8; 1.7, 1.7*, 1.6*	
Epididy	0.75; 0.76, 0.72, 0.65*	
Spleen	0.46; 0.45, 0.48, 0.49	0.31; 0.34, 0.34, 0.37

GROSS (10/s/g):
Amorphous: (uterus dilatation) 0; 3,3,2
Crystalline: (" ") 1; 0,0,2

HISTOPATHOLOGY (10/s/g):

Amorphous	**MALES**	**FEMALES**
LIVER	0; 10,30,100 mkd	0; 10,30,100 mkd
Atrophy	0 0 0 4	No data
Atypia	0 2 6 10	0 1 5 9
Fatty change	0 0 0 2	No data
Hyperplasia	0 4 7 10	0 0 3 4
Single cell necrosis		0 0 1 1

13-WK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN RATS (0,10,30,100 mkd)

Crystalline	**MALES**	**FEMALES**
	0; 10,30,100 mkd	0; 10,30,100 mkd
LIVER		
Atrophy	0 0 0 1	0 0 0 1
Atypia	0 2 8 10	0 1 2 10
Fatty change	0 0 0 2	0 0 0 2
Hyperplasia	0 2 4 9	0 2 2 6
Single cell necrosis	2 0 3 5	0 0 1 1
Infiltrate, mononuclear		0 1 1 2
EPIDIDYMIS		
Aplasia, aspermia	0 0 0 2	
LUNG		
Infiltrate, foamy macrophages		0 0 0 2

13-WEEK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN MICE (vol 1.56)
RR 745-02436. May 1995. Parke-Davis.
Lots: XH020193 (amorphous form) and XH020195 (crystalline form)

TREATMENT: Seven groups of B6C3F1 mice (8 weeks old; 3/s/g for controls and 52/s/g for treated with 10/s/g for toxicology and rest for PK;). Mice were given by oral gavage in 0.5% methylcellulose, **0, 100, 200, or 400 mg/kg/day**. A previous study had shown differences in toxicity between lots in mice . In DW 13, blood samples were collected by cardic puncture from 6 mice/time point at 0, 0.5, 2, 4, 8, 12, and 24 hours. Samples were collected from controls 0.5 hours postdose (3/s).

RESULTS
MORTALITY: 13 (all designated for toxicokinetic phase "so only cursory gross necropsies were performed." Four died after being caught in feeder; 1 control (ovarian mass); 8 unknown causes.
Control: ovarian mass
Caught in feeder: 2 (one amor & one cryst. 100 mkd; one @ 400 mkd crys and one amorph);
Unknown (amorphous): 1@ 100; 3@ 400 mkd
(crystalline): 2@ 200; 1@ 400 mkd

Amorphous (6 females): 2 LD, 4 HD
Crystalline (3 males & 3 females): 2 LD males, 1 MD male; 1 MD female; 2 HD females

13-WEEK ORAL TOXICITY (AMORPHOUS/CRYSTAL) IN MICE (0,100,200,400)
CLINICAL SIGNS: "None drug-related"
BODY WEIGHTS: No drug effects

FOOD CONSUMPTION: No drug effects

OPHTHALMOLOGY: No drug effects (no data)

HEMATOLOGY (*p<0.01):

Amorphous: **0; 100, 200, 400 mg/kg**

Myeloid: erythroid ratio (bone marrow) down		(HD male)
WBC (10^9/L):	5.36; 5.22, 6.42, 8.86*	(female)
Neutrophils (10^9/L):	0.74; 0.62, 1.12*, 1.24*	(female)
Lymphocytes (10^9/L):	4.3; 4.4, 5.0, 7.2*	(female)

Crystalline

WBC (10^9/L):	3.8; 4.4, 5.4, 6.5*	(male)
Lymphocytes (10^9/L):	2.8; 3.4, 4.4, 5.2*	(male)
Myeloid: erythroid ratio	3.8; 2.7, 2.5, 2.1*	(male)
	3.4; 2.2*, 2.3*, 2.3*	(female)
Erythroid series (10^9/femur)	2.8; 3.9, 4.0, 5.2*	(male)
Eosinophils (%):	3.3; 2.6, 2.2, 1.5*	(female)
Eosinophils (10^9/L):	0.20; 0.16, 0.12, 0.12*	(female)
Myeloid maturation index:	15; 9.2*, 9.7*, 9.4*	(female)

CLINICAL CHEMISTRY ((0,100,200,400;*p<0.01)

Amorphous	**MALES**	**FEMALES**
TG (mg/dl):	160; 95, 93, 89*	130; 100, 110, 100
ALKP (IU/L)	120; 130, 130, 160*	160; 180, 180, 230*
Total CPK	460; 300, 230, 160*	610; 74, 210, 200
Pi (mg/dl)	8.8; 10.9, 11.4, 10.9	8.4; 9.7, 12*, 11.4*
ALT (IU/L)	146; 68, 57, 96	50; 54, 59, 66*
T. Bilirubin (mg/dl)	0.50; 0.58, 0.50, 0.50	0.50; 0.38, 0.82, 0.62*
Chloride (mEq/L)		116; 119, 121, 124*
Sodium (mEq/L)	150; 151, 150, 153	152; 158, 162*, 164*

13-WEEK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN MICE (0,100,200,400 mkd)

Crystalline

CLINICAL CHEMISTRY (*p<0.01)

	MALES	FEMALES
	0; 100, 200, 400 mg/kg	**0; 100, 200, 400 mg/kg**
Glucose (mg/dl)	N.D.; 210, 166*, 157*	N.D.
Pi (mg/dl)	8.8; 9.9, 11.1, 12*	8.4; 9.5, 12*, 12.4*
Ca (mg/dL)	No effects	10.6; 10.8, 11.6*, 12.0*
Chloride (mEq/L)	" "	116; 119, 127*, 129*
Sodium	" "	152; 156, 166, 172
TG (mg/dl)	160; 120, 93*, 88*	130; 100, 100, 90
ALKP (IU/L)	120; 130 140, 150*	160; 190, 200* 220*
Albumin (g/dl)	3.0; 2.8, 2.7*, 2.7*	
Creatinine (mg/dl)	N.D.; 0.28*, 0.20*, 0.20*	
Urea N (mg/dl)	N.D.; 31*, 22*, 21*	
T. Protein (g/dL)		5.6; 5.5, 6.0, 6.3*
Albumin (g/dL)		3.1; 2.9, 3.4, 3.6*

PATHOLOGY

ORGAN WEIGHTS ((0,100,200,400 mkd; % brain wt;* p<0.01)

Amorphous	MALES	FEMALES
	0; 100, 200, 400 mg/kg	**0; 100, 200, 400 mg/kg**
Lung	0.396; 0.453*, 0.461*, 0.536*	
Liver	2.91; 2.99, 3.06, 3.26*	2.74; 2.93, 3.16*, 3.11*
Crystalline		
Heart	0.31; 0.30, 0.33, 0.33*	
Lung	0.396, 0.406, 0.495*, 0.494*	
Adrenal	0.022; 0.025, 0.043, 0.041*	
Liver	2.91; 2.995, 3.096, 3.282*	2 74; 2.79, 2.98, 3.09*
Spleen	0.14; 0.14, 0.144, 0.16*	

GROSS : No findings

13-WK ORAL TOXICITY (AMORPHOUS/CRYSTAL) IN MICE (0,100,200,400 mkd)
HISTOPATHOLOGY

Amorphous

Adrenal: Single cell necrosis, multifocal 0; 1, 0, 3 (Females)

	MALES **0; 100, 200, 400 mg/kg**	FEMALES **0; 100, 200, 400 mg/kg**
ESOPHAGUS		
muscular degeneration	0; 2, 1 4	3; 2 2 2
LIVER (severity and extent increased as a function of dose)		
Atypia, nuclear, hepatocyte,	1; 3, 4, 10	0; 0, 0, 3
Basophilia, periportal	0; 1, 5 5	0; 0, 0, 0
Decreased rarefaction	1; 10, 10, 9	0; 3, 3, 2
Mitosis increased	0; 4, 9, 8	1; 2, 2, 4
Necrosis, single cell	4; 10, 10, 10	7; 10, 10,10
Nuclear alteration		
Anisokaryosis	0; 5, 6, 8	0; 0, 1, 0
LYMPH NODE infiltrate	0; 2, 2, 4	0; 6, 7, 2
VAGINA infiltrate		1; 0, 1, 3

Crystalline ((0,100,200,400 mkd; 10/s/g)

ADRENAL:		
Single cell necrosis, multifocal		0; 1, 0, 3
Multinucleated cells x-zone		0; 0, 0, 2
LIVER (severity and extent increased as a function of dose)		
Atypia, nuclear, hepatocyte,	1; 5, 7, 10	0; 1, 0, 3
Basophilia, periportal	0; 2, 2, 5	0; 0, 0, 0
Decreased rarefaction	1; 9, 8, 10	0; 3, 5, 6
Mitosis increased	0; 1, 3, 4	1; 1, 1, 1
Necrosis, single cell	5; 10, 10, 10	7; 8, 6, 9
Nuclear alteration		
(Anisokaryosis)	0; 4, 7, 9	0; 1, 0, 2
VAGINA infiltrate		1; 1, 1, 3
LYMPH NODE (medullary sinus)		
Multinucleated cell	0; 1, 3, 5	0; 2, 7, 9
Necrosis	0; 0, 0, 0	0; 0, 3, 2

2-YEAR DOG TOXICITY STUDY (vol 1.43) (AMORPHOUS FORM)
RR 745-02334. Parke-Davis. June 1992-June 1994.
Lot#s: XH350891 (90.3% active but 98% pure vol 1.44, p.626; used until January 31, 1993)
XH030193 (90.8% active; used until June 1994)

TREATMENT: Eight groups of beagles (10/s/g; 11-15 months of age) were given by capsule, **0, 10, 40, or 120 mg/kg/day**. The first **3/s/g were killed after 52 weeks and 5/s/g were killed after 104 weeks dosing. Two/s/g were withdrawn after 52 weeks and given a 14 week recovery** period before necropsy. Plasma for CI-981 levels was taken weeks 24, 50, 76, and 102 predose and 1, 2, 4, 8, 12, and 24 hours postdose. Semen was collected weeks 50, 51, 52, 64, 78, 91, 104 "when possible".

EM of liver sections was performed on 120 mg/kg dogs (moribund dog; week 7, week 52, n=4; week 104-all dogs) and "selected controls" in week 52 (n=2) and week 104 (n=3).

There were "periodic reductions in daily food rations" (usual was 320-350g) in 3 control females, 3/s at 10 mkd, one male at 40, and 3 females at 120 mkd from week 61-104 due to "clinically overweight condition as ascertained by clinical veterinary staff".

RESULTS
MORTALITY: Two males at 120 mkd (#4296 and #4299); euthanatized weeks 7 and 9

CLINICAL SIGNS:
FIRST YEAR

	MALE				FEMALE			
SIGN	**0 mkd**	**10 mkd**	**40 mkd**	**120 mkd**	**0 mkd**	**10 mkd**	**40 mkd**	**120 mkd**
Emesis	70	107	126	170	71	54	67	199
Feces red	9	3	20	74	14	6	6	66
Diarrhea	19	6	45	100	11	17	12	103
Salivation	0	0	51	131	0	0	0	277

2-YEAR DOG TOXICITY STUDY (vol 1.43) (AMORPHOUS FORM)
SECOND YEAR

	MALE (doses, mkd)				FEMALE (doses, mkd)			
SIGN	**0**	**10**	**40**	**120**	**0**	**10**	**40**	**120**
Emesis	20	64	42	11	47	11	11	90
Red feces	0	0	2	5	9	2	1	34
Diarrhea	6	3	9	8	11	1	1	35
Salivation	35	8	0	79	0	0	26•	131

TONIC CONVULSIONS:
One male at week 38 (120 mkd)
One male at week 96 (10 mkd) and ataxic for several minutes thereafter

PROSTRATE with bloody emesis in cage: one male in week 39 (10 mkd)

BODY WEIGHT GAIN: "No statistically significant differences" either years 1 or 2

FOOD CONSUMPTION: No drug effects

OPHTHALMOLOGY: Prominent vitreal strands in both eyes (one 120 mkd female)
Bilateral lenticular opacities: 2 male controls; 1 male and 2 females at 10 mkd

HEMATOLOGY: "No clinically significant changes in hematology parameters occurred."
Nothing significant at *p<0.05 except:
Week 52:
HCT decreased from 47.8 to 45.3 (HD F)
Eosinophils (%) increased 1.9; 2.9, 4.9*, 4.8* (females)

Week 78
Eosinophils (%) increased 2.2; 2.2, 5.2*, 6.6* (females)

2-YEAR DOG TOXICITY STUDY (vol 1.43) (AMORPHOUS FORM)
BONE MARROW: "No clinically significant changes in bone marrow parameters occurred."

Week 52

MALE DOGS	**0 mkd**	**10 mkd**	**40 mkd**	**120 mkd**
Erythroid mat. index	3.2	3.6	3.8	4.0*
Myeloid mat. index	12.6	11.4	11.2	8.4*
FEMALE DOGS				
Erythroid mat. index	3.7	4.1	3.7	3.2*
Myeloid mat. index	10.3	13	8.9	8.2

*p<0.05

Week 104

MALE DOGS	**0 mkd**	**10 mkd**	**40 mkd**	**120 mkd**
erythroid mat. index	2.6	2.8	2.7	2.8
Myeloid mat. index	12.8	13.7	12.1	10.4*
FEMALE DOGS				
erythroid mat. index	3.7	4.1	3.7	3.2*
Myeloid mat. index	13.1	13.2	10.0	8.9*
M:E ratio	1.5	1.8	1.2	1.1*

*p<0.05

EKG: "no drug-related changes in heart rate or ECG parameters" (no summary table)

BLOOD PRESSURE & BODY TEMPERATURE:
"no drug-related effects" (no summary table)

CLINICAL CHEMISTRY (*p<0.05)
Males (0,10,40,120 mkd):
Cholesterol, HDL, non-HDL: all treated decreased significantly (but 40 and 120 mkd same)
Cholesterol (mg/dl): 134; 101*, 80*, 82* (week 104)
HDL (mg/dl): 113; 88*, 69*, 70* (week 104)
TG (mg/dl): decreased transiently M and HD (back to control level at week 78)
ALKP (IU/L): increased M and HD weeks 26-65; also up rest of study but large SE.

2-YEAR DOG TOXICITY STUDY (vol 1.43) **(Amorphous form; 0,10,40, 120 mkd)**

CLINICAL CHEMISTRY (*p<0.05)

Females (0,10,40,120 mkd):

Cholesterol (mg/dl): 158; 123, 98, 78*
HDL (mg/dl): 141; 106, 89, 69*
Non-HDL 18; 17, 9.4, 8.4*
ALT increased M and HD (1.5x)
AST: increased transiently M and HD (2x)
ALKP (IU/L): increased throughout study in HD (2x)
CPK (total meq/L; muscle isozyme): increased (up more times and higher in all treated, as a function of dose)

URINALYSIS:

"No clinically significant changes from control or pretest were seen." (specific gravity and pH)
"Red-colored urine in one male @ 10 mkd (weeks 14 and 24) due to occult blood"

LENS BIOCHEMISTRY (0,10,40, 120 mkd; *p<0.05): week 52

Males

Glucose: umol/g ww: 5.64; 5.47, 4.18*, 4.7*
nmol/mg protein: 15.1; 12.6, 10.4, 10.7
Potassium (nomol/mg protein): 190; 183, 168, 156

SEMEN ANALYSES (mean±SE; *p<0.05):

No effects on count, concentration, morphology, motility

Week 64 reversal (very variable data):
Normal (%): 37±31; 6.0±1.0, 36±27, 10.5± 1.5

SPERM ANALYSIS (week 50, vol.; week 64, % abnormal; wk.78, % normal)

	control	**10 mkd**	**40 mkd**	**120 mkd**
Sperm volume (%)	7.0±0.95	6.7± 0.54	5.8± 0.87	5.3± 0.59
Abnormal heads (%)	5.4±2.6	2.0 ± 0.8	0.8 ± 0.6	18 ± 13
Normal heads (%)	27± 14	28 ±8.7	30± 15	16± 0.00

2-YEAR DOG TOXICITY STUDY (vol 1.43) **(Amorphous form; 0,10,40, 120 mkd)**

PATHOLOGY

ORGAN WEIGHTS (*p<0.05; % of BW)

1-year sacrifice

Lung, adrenal, and prostate increased in HD Males
Heart and adrenal in HD females

Terminal sacrifice

Testes (%brain wt) 0.172; 0.167, 0.221*, 0.235* and % BW and grams
Adrenal (females; % BW): 0.016; 0.014, 0.018, 0.020*

GROSS (0,10,40, 120 mkd)

Dogs that died (n=2 HD males)

Adrenal: abnormal color, thin cortex
Gallbladder: thick, abnormal color & content
Large intestine, colon, cecum: abnormal color
Mesenteric lymph node: abnormal color, enlarged
Liver: abnormal surface, color

1-year sacrifice (3/s/g)

Large intestine: abnormal color (2/3 HD females)
Small intestine: " " (1/3 HD females)
Mesenteric lymph node

Abnormal color	0; 0, 2, 0 M	0; 0, 1, 3 F
Enlarged	0; 0, 0, 0 M	0; 0, 0, 2 F

Reversal sacrifice (2/s/g)

Kidney abnormal color ½ HD male and female

2-year sacrifice (5/s/g except HD males = 3/g)

Large intestine abnormal color 1 HD females
Liver abnormal texture 0; 0, 1, 1 F
Small intestine abnormal color duodenum 1 HD male and 1 HD female

2-YEAR DOG TOXICITY STUDY (Amorphous form; 0,10,40, 120 mkd)

HISTOPATHOLOGY

DOGS THAT DIED (n=2 males at 120 mkd)

Adrenal: hemorrhage, necrosis, fibrosis, vacuolation z. reticularis

Gallbladder: degeneration eppithelial cell, edema, hemorrhage, mucosa; ulcer, thin mucosa, necrosis venule

Large intestine: hemorrhage upper mucosa

Liver: fibrosis, common bile duct muscularis, infiltrate neutrophilic central vein; bile duct hyperplasia

Small intestine: blunting villus

Tongue: myocyte degeneration, mononuclear infiltrate; regeneration myocyte

Mesenteric lymph node: hemorrhage, hemosiderin

Testis: degeneration seminiferous tubule ½

Epididymis: cellular debris ½

(Psoas muscle, bone marrow: no effects)

1-YEAR SACRIFICE (0,10,40, 120 mkd; 3/s/g)

Adrenal: Fibrosis z. Reticularis 0; 0, 1, 3 (Females)

Gallbladder: Hemorrhage mucosa 1 (HD Male)

Large intestine: Hemorrhage upper mucosa 1 (HD Male)

Liver	**MALE**	**FEMALE**
Granuloma:	0; 2 1 1	0; 0, 0, 2
Bile stasis:	0; 0, 2, 1	0; 0, 0, 3
Hyperplasia bile duct	0; 0, 1, 0	0; 0, 0, 2
Lymphocyte infiltrate central vein	0; 1, 0 3	0; 2, 3, 2

Small intestine:

Congestion villus	1 HD male	
Single cell necrosis duodenum	1 HD male	

Mesenteric lymph node:

Hemorrhage:	0; 0, 0, 1	0; 0, 1, 3
Hemosiderin		0; 0, 0, 2
Edema		0; 0, 1, 2

Brain

Infiltrate mononuclear	cerebrum	1 HD M
	medulla	1 HD M
	pons	1 MD F

2-YEAR DOG TOXICITY STUDY (0, 10,40, 120 mkd)
REVERSAL SACRIFICE (2/s/g):

Brain dilatation 1 HD male

Liver

Pigmentation multifocal, mild		0; 1, 0, 2
Granuloma	0; 1, 0, 1	0; 0, 1, 1

2-YEAR SACRIFICE (5/s/g except HD males = 3):

Liver

Granuloma:	4; 5 4 3 M	4; 5, 5, 5 F
Bile stasis:	0; 0, 2, 1	0; 0, 3, 5
Fibrosis central vein	0; 0, 3, 0	0; 1, 0, 3

Brain choristoma 1 HD M

Choristoma= "a mass of tissue histologically normal for an organ or part of the body other than the site at which it is located; called also aberrant rest and heterotopic tissue."

1-YEAR ORAL TOXICITY STUDY IN RATS
RR 764-02288. November 1992 to November 1993. Parke-Davis
Lot #: XH080292 (through 1/93) then lot# XH030193
TREATMENT: Four groups of Wistar (BR) rats (6-7 weeks old at receipt; 8/s/g for plasma drug determinations at week 26; 10/s/g for week 26 interim necropsy; 15/s/g for week 52 terminal necropsy) were given by oral gavage in 0.5% methylcellulose, **0, 5, 70, or 125 mg/kg/day**.

RESULTS
MORTALITY: 2 (control); 5 (5 mkd); 4 (70 mkd); 5 (125 mkd)
None are stated to be due to drug; 7 were stated to be gavage accidents

CLINICAL SIGNS:

DOSE	TONIC-CLONIC CONVULSIONS		RED-STAINING	
	Male	Female	Male	Female
0 mkd	0	0	0	0
5 mkd	1	1	2	0
70 mkd	2	2	1	0
125 mkd	0	0	3	0

1-YEAR ORAL TOXICITY STUDY IN RATS (Amorphous form; 0,5,70,125 mkd)
BODY WEIGHT GAIN ($p \leq 0.01$):
Males: transient significant decrease weeks 3-9 in HD (5%); remaining time same as controls.
Females: transient signficant increase weeks 9-25 HD (5%)

FOOD CONSUMPTION($p \leq 0.01$):
Males: no significant effects
Females: significant increases in MD and HD (weeks 4-29)

HEMATOLOGY: no drug effects
BONE MARROW: no signficant effects
BIOCHEMISTRY (*$p<0.01$):

	MALES **0, 5, 70, or 125 mg/kg/day**	FEMALES **0, 5, 70, or 125 mg/kg/day**
Total protein (g/dl):	6.4; 6.2, 6.1, 6.1*	
Sodium (meq/L):	150; 150, 151, 152* (wk 52)	
Chloride	104; 105, 106*, 107* (wk 26) 102; 103, 104, 105* (wk 52)	
TG (mg/dl)	122; 89, 64*, 71* (wk 52)	
Glucose (mg/dl)		141; 168, 164, 197* (wk 26) 155; 177, 159, 166 (wk 52)
Cholesterol (mg/dl)		64; 67, 100, 101* (wk 26) 99; 111, 182* 181* (wk 52)
Total bilirubin (mg/dl)		0.3; 0.2, 0.2, 0.2* (wk 52)
Creatinine (mg/dl)		0.7; 0.7, 0.7, 0.6* (wk 26) 0.8; 0.7, 0.7*, 0.6* (wk 52)
CPK (IU/L)		360; 300, 270, 240* (wk 52)
LDH (IU/L)		270; 220, 160, 130* (wk 26) 430; 400, 290, 210* (wk 52)
AST (IU/L)		140; 110, 85* 19* (wk 52)

URINALYSIS (*$p<0.01$):
pH 6.1; 6.2, 6.5*, 6.9* (females wk 52)

1-YEAR ORAL TOXICITY STUDY IN RATS (Amorphous form; 0,5,70,125 mkd)
PATHOLOGY

ORGAN WEIGHTS (% BW and % brain wt; *p<0.01):

Males: 26 weeks: no effects 52 weeks: Adrenal and Liver increased in HD
Females: 26 weeks: Liver increased HD 52 weeks: Liver increased HD

GROSS PATHOLOGY 26 weeks: 1/9 HD females had enlarged adrenal

HISTOPATHOLOGY (week 26) Control and HD exam except liver (all doses)

	Males					Females				
	0	5	70	125	mkd	0	5	70	125	mkd
LIVER No.	10	10	9	10		10	10	10	9	
necrosis, single cell	0	0	0	4		0	0	0	0	
cellular atypia	0	0	8	10		0	0	6	9	
fatty change	0	0	1	2		0	0	0	0	
bile duct hyperplasia	0	1	1	9		1	1	2	3	
KIDNEY										
dilatation tubule medulla (nd = not determined)	0	nd	nd	0		1	nd	nd	3	

HISTOPATHOLOGY (week 52)

Control and HD exam except liver (all doses); kidney, thymus, stomach, spleen (0,M,HD) (nd = not determined) (does not include dying/moribund sac.)

	Males					Females				
	0	5	70	125	mkd	0	5	70	125	mkd
No.	13	14	12	13		15	12	15	13	
LIVER										
cellular atypia	0	0	8	11		0	0	15	10	
THYMUS hemorrhage	1	nd	0	5		0	0	1	1	
bile duct hyperplasia	5	7	4	3		2	3	4	6	
necrosis, liquefactive	6	9	1	0		1	0	0	0	
UTERUS stromal polyp						0	nd	2/3	2	
HARDERIAN Gland										
porphyrin pigment	0	nd	nd	3		0	nd	nd	3	
KIDNEY										
glomerulonephropathy (stage 2)	2	2	0	1		0	0	3	5	

2-YEAR CARCINOGENICITY STUDY IN WISTAR RATS (Vol. 1.52)
RR 745-02392. April 1993- April 1995. Parke-Davis, Ann Arbor
Lot #s: XH030193 (week 0-68; 91% active) and XH020193 (week 68-104; 93% active)

TREATMENT: Five groups of Wistar rats (65/s/g; 8-9 weeks old) were given by oral gavage in 0.5% methylcellulose, **0, 0, 10, 30, and 100 mg/kg/day of the amorphous form**. Plasma for drug determinations was obtained from 3/s/g (control) and 6/s/g (treated) during week 52. "All pathology data were subjected to peer review for determination of accuracy and interpretation" including a second microscopic review. "The narative generated by the study pathologist was also reviewed for consistency of interpretaions and conclusions...Discrepancies between original and review diagnoses and all tumors of liver were reviewed by a Pathology Review Group consisting of a consultant, Dr. J.A. Swenberg..." plus 3 staff pathologists plus the study and review pathologists and the director of pathology (n=7). Data "represent consensus diagnoses."

RESULTS
MORTALITY
Survival at 104 weeks: 36, 31, 51, 34% (males) and 41, 42, 45, 49% (females)
(combined controls and 10, 30, 100 mkd)
"A number of deaths...attributable to gavage error based upon gross pathological findings, i.e., **ruptured esophagus**."
5, 4, 13, 8, 14 (males) 0, 0, 1, 3, 3 (females)

Yet, p.71: Gross intercurrent deaths lists only:
Perforation thoracic esophagus: 1 LD male
Rupture esophagus 1 HD F

CLINICAL SIGNS: "similar in all groups" (no data)

BODY WEIGHT GAIN: no biologically significant effects

FOOD CONSUMPTION: no biologically significant effects

OPHTHALMOLOGY: "no effects" (no data)

2-YEAR CARCINOGENICITY STUDY IN WISTAR RATS (0,0,10,30,100 mkd)
HEMATOLOGY (RAT CA STUDY)

	MALES				**FEMALES**			
Dose (mkd)	**0**	**10**	**30**	**100**	**0**	**10**	**30**	**100**
MCH	18.6	18.7	18.2	17.6*	19.3	19.3	19.3	19.1
MCHC	32	32	31	31*	31	31	31	31
RBC	7.7	7.2	7.9	7.7	7.6	7.5	7.5	7.1*
HGB	14.3	14.3	14.4	13.5	14.7	14.5	14.5	13.6*
HCT	45	42	46	44	47	46	46	44*
Eosinophil (%)	2.6	3.8	3.2	2.3	2.0	3.8	3.2	2.9*

ORGAN WEIGHTS TERMINAL SACRIFICE (% body wt; *p<0.01; brain,kidney,liver)
KIDNEY: 0.98; 1.04, 0.873, 0.870* (male)
LIVER: 3.46; 3.70, 3.70, 4.05* (female)

GROSS:
INTERCURRENT DEATHS: no drug effects
TERMINAL SACRIFICE (n= 26; 23; 21; 30, 20, 27 males & 23, 30; 27, 29, 32 females)
Pituitary: focus 2, 1; 4, 4, 7 (females)
Liver focus: 3, 4; 4, 5, 8 (females)

2-YEAR CARCINOGENICITY STUDY IN WISTAR RATS (0,0,10,30,100 mkd)
HISTOPATHOLOGY

INTERCURRENT DEATHS:

LIVER fatty change: 4, 4; 0, 3, 14 (males)

Non glandular STOMACH hyperkeratosis 0, 1; 4, 6, 14 (males); 4; 1; 4, 2, 5, 8 (females)

TERMINAL SACRIFICE: n= 26; 23; 21, 30, 20, 27 (males); 23, 30; 27, 29, 32 (females)

	Males	Females
LIVER	**0,0,10,30,100 mkd**	**0,0,10,30,100 mkd**
Focus of cellular alteration, basophilic tigroid	1, 0; 4, 6, 17	7, 12; 11, 10, 23
Adenoma hepatocyte	4, 0; 1, 0, 2	2, 2; 2, 3, 7
Atypia cellular	2, 1; 4, 19, 21	2, 1; 5, 15, 32
Vacuolation, cytoplasmic, hepatocyte	1, 3; 4, 5, 5	1, 6; 1, 5, 12
Biliary cyst	1, 1; 3, 3, 5	3, 2; 5, 3, 7
SKELETAL MUSCLE atrophy fiber	5; 5, 4, 9, 2	0, 0; 1, 1, 4
SKIN lipoma	2, 0; 0, 0, 0	0, 0; 1, 2, 2

Sponsor's analysis:
2-YEAR CARCINOGENICITY STUDY IN WISTAR RATS (0,0,10,30,100 mkd)

	DOSE (mg/kg)				
Tumor type	**0 mkd**	**10 mkd**	**30 mkd**	**100 mkd**	p-value (peto test)
lipoma of kidney	0	0	0	1	0.044
adenocarcinoma large intest	0	0	0	1	0.044
adenocarcinoma preputial gl	0	0	0	1	0.043
myxoma of skin	0	0	0	1	0.047
thymoma (malignant)	0	0	0	1	0.047
adenoma of parathyroid*	0	0	0	1	0.031
all tumors skeletal muscle*	0	0	0	2	0.007

* females only; rest in males only

2-YEAR)GENICITY STUDY IN B6C3F1 MICE (Vol. 1.47)
RR 745-(ptember 1993- October 1995. Parke-Davis, Ann Arbor
Lot #s: XH030193 (week 0-68; 91% active) and XH020193 (week 68-104; 93% active)
TREATMENT: Six groups of B6C3F1 mice (65/s/g; 8 weeks old) were given by oral gavage in 0.5% methylcellulose, **0 (vehicle), 0 (untreated), 100, 200, 400, and 800 mg/kg/day of the amorphous form**. Blood for drug determinations was obtained from 10/s/g during week 100.

RESULTS
High dose termination (800 mkd group)
RR 745-02315. September 1993- Janu- 1994. Parke-Davis.

MORTALITY (first two weeks):
Males: 13 died
Females: 25 died

The 800 mkd group was terminated after 13 weeks due to high mortality. The first ten males and females surviving to week 9 were killed after 13 weeks for histopathology; the remaining were killed during week 10.

CLINICAL SIGNS (mice that died): coolness to touch, decreased feces, hypoactivity, weakness, hunched posture, decreased skin turgor, thinness.
(mice that lived, 18 males and 8 females): one or more of above, mainly weeks 1-4

BODY WEIGHT GAINS: not significantly different from controls

FOOD CONSUMPTION: transient decreases in males (week 1) and females (weeks 1-3)

2-YEAR CARCINOGENICITY STUDY IN B6C3F1 MICE (0,0,100,200,400,800 mkd)
(EARLY TERMINATION OF 800 mg/kg DOSE AT 13 WEEKS; amorphous form)

PATHOLOGY

GROSS (early death; 800 mkd)

STOMACH: thickening of non-glandular stomach in 13/25 females
impaction in 7/13 males and abnormal content in 6/13
THYMUS: small in 3/25 females

GROSS (13-week; 800 mkd) : no findings

HISTOPATHOLOGY (early death; 800 mkd)

ADRENAL: atrophy, zonal x-zone 25/25 females
congestion x-zone 4/25
decreased fine vacuoles, z. fasiculata, cortical cell 13/13 males & 21/25 females

LIVER: degeneration, vacuolar (cannot get total numbers affected)
necrosis
nuclear alteration, anisokaryosis

STOMACH (non-glandular): hyperkeratosis, hyperplasia, mucosal erosion

SKELETAL MUSCLE degeneration in 1 male and 5 females
TESTIS degeneration, epithelium in 3/13 males

HISTOPATHOLOGY (13-week sacrifice; 800 mkd)

ADRENAL: decreased fine vacuoles, z. fasiculata, cortical cell 2 males
ESOPHAGUS: degeneration in 2 females
LIVER: hypertrophy in all
nuclear alteration, anisokaryosis in 9 males
nuclear alteration, karyomegaly in all males/females

MAIN STUDY (2-years at 0,0; 100, 200, 400 mkd)
MORTALITY:

Survival at 104 weeks: 89, 78, 88, 74, and 68% (males) and 72, 77, 75, 72, and 72% (females) for the 0, 100, 200, and 400 mkd groups.

CLINICAL SIGNS: alopecia in all groups "common finding in mice"
"Most of untreated control animals convulsed upon handling..." (This needs checking)

2-YEAR CARCINOGENICITY STUDY IN B6C3F1 MICE (0,0,100,200,400 mkd)
BODY WEIGHT GAIN: no biologically significant effects

FOOD CONSUMPTION: no biologically significant effects

OPHTHALMOLOGY: "no effects" (no data)

HEMATOLOGY (*p<0.01)

	FEMALE MICE				
	0 (VC)	**untx**	**100 mkd**	**200 mkd**	**400 mkd**
RBC	9.035	8.842	8.784	8.415	8.655*
HGB	14.3	14.0	14.0	13.5	13.8*
HCT	47.5	46.3	46.5	45.1	45.78*

ORGAN WEIGHTS (% brain wt; *p<0.01) TERMINAL SACRIFICE
KIDNEY: 1.70; 1.65, 1.593*, 1.57*, 1.61* (male)
LIVER: 3.57; 3.78. 4.23, 5.54, 3.36* (male)

GROSS (terminal; 100, 200, 400 mkd): no findings
INTERCURRENT DEATHS [n=7, 14, 8, 17, 21 (M) and 18, 15, 16, 18, 18 (F)]
No drug effects

TERMINAL SACRIFICE [n= 58; 51; 57; 48, 44 (males) & 47, 50; 49, 47, 47 (females)]
No drug effects

HISTOPATHOLOGY (non-neoplastic)
INTERCURRENT DEATHS: no drug effects

HISTOPATHOLOGY (non-neoplastic)
TERMINAL SACRIFICE [n= 58; 51; 57; 48, 44 (males) & 47, 50; 49, 47, 47 (females)]

2-YEAR CARCINOGENICITY STUDY IN B6C3F1 MICE (0,0,100,200,400 mkd)
HISTOPATHOLOGY (terminal;100, 200, 400 mkd; 10/s/g)

Heart: fibrosis interventricular septum

FEMALES				
0	**0**	**100**	**200**	**400**
0	1	1	2	5

Esophagus: Degeneration muscularis

MALES					FEMALES				
0	**0**	**100**	**200**	**400**	**0**	**0**	**100**	**200**	**400**
1	0	3	1	3	0	0	2	3	3

Esophagus: Fibrosis, muscularis

MALES					FEMALES				
0	**0**	**100**	**200**	**400**	**0**	**0**	**100**	**200**	**400**
0	2	10	8	5	0	4	8	2	3

Skeletal muscle: Degeneration

0	**0**	**100**	**200**	**400**	**0**	**0**	**100**	**200**	**400**
2	3	1	4	23	1	2	3	1	25

Eye degeneration optic nerve: 1 female at 200 mkd

Liver

Focus of cellular alteration, clear cell: 0; 1; 6, 13, 12 (males)
1; 1; 1, 5, 6 (females)
Focus of cellular alteration, basophilic 3; 1; 4, 6, 12 (males)
1; 2; 3, 1, 3 (females)
Focus of cellular alteration, eosinophilic 3; 7; 11, 21, 35 (M)
3; 2; 1, 4, 5 (F)
Atypia cellular 0, 0, 0, 0, 4 (males) 0, 0, 0, 0, 1 (females)

Mammary gland

Cystic dilation duct 0; 0; 0, 0, 1 (males) and 1; 2; 3, 2, 5 (females)

2-YEAR CARCINOGENICITY STUDY IN B6C3F1 MICE (0, 100,200,400 mkd)
HISTOPATHOLOGY (neoplastic)
Liver

ADENOMA

MALES					FEMALES				
0	**0**	**100**	**200**	**400**	**0**	**0**	**100**	**200**	**400**
17	19	15	21	33	4	6	2	9	2

CARCINOMA

MALES					FEMALES				
0	**0**	**100**	**200**	**400**	**0**	**0**	**100**	**200**	**400**
8	16	15	21	20	0	2	1	1	9

HEMATOPOIETIC TISSUE
LYMPHOMA

MALES					FEMALES				
0	**0**	**100**	**200**	**400**	**0**	**0**	**100**	**200**	**400**
2	2	1	2	6	8	7	13	19	12

TUMOR ANALYSES (sponsor's analysis):

Males	direction trend	2-tailed p value (Peto)
All tumors:	+	0.005
Hepatocyte adenoma	+	0.001
Females		
Hepatocyte carcinoma	+	0.002

"The Tarone test confirmed the Peto results ($p<0.01$) for all 3 categories."

PERINATAL-POSTNATAL STUDY IN FEMALE RATS

RR 745-02283. September 1993. Parke-Davis.

TREATMENT: Four groups of sperm-positive Sprague-DawleyCD rats (30/g; 12-13 weeks old) were given **0, 20, 100, or 225 mg/kg/day** by gavage in 0.5% methylcellulose beginning **gestation day 7 and continuing through lactation day 20.** All Fo were allowed to deliver and wean their offspring. Mated F1 females underwent cesarean section on gestation day 21.

RESULTS

Fo:

Clinical signs: hypoactivity, hypothermia, dehydration: 2 HD

Euthanized (with no pups remaining on postpartum days 1-10): 10 HD

Found dead: 2 HD

Body weight gain: HD 14% less than control (gestation) but 2x greater (lactation)

Food consumption: HD 8% less than control (gestation) and 23% less (lactation)

GROSS PATHOLOGY (FO):

Liver

abnormal color and reticular pattern: 2 HD

Stomach

Abnormal color (glandular stomach): 3 HD

Abnormal surface (nonglandular stomach): 4 HD

REPRODUCTIVE PARAMETERS (*p<0.05):

Stillborn and dead pups on postnatal day 0: 0.2; 0.1, 0.5, 1.0* (no./litter)

No effects on gestation duration, liveborn, litter size, implant sites, postimplantation loss

F1 Survival (%)

	0 mkd	**20 mkd**	**100 mkd**	**225 mkd**
Birth	98.7	97.0	95.8	94.0*
Neonatal	98.7	98.4	96.4	63.3*
Weaning	100	98.3	100	55.4*

F1 Body weight (Male)

Weight (g)	**0 mkd**	**20 mkd**	**100 mkd**	**225 mkd**
postnatal day 0	6.4	6.6	6.4	5.8*
4	10.2	10.4	9.2*	7.2*
21	57.4	58.0	49.4*	40.5*

PERINATAL-POSTNATAL STUDY IN RATS (0, 20, 100, or 225 mg/kg/day)

F1 Body weight (Female)

Weight (g)	0 mkd	20 mkd	100 mkd	225 mkd
postnatal day 0	6.1	6.3	6.0	5.4*
4	9.6	9.6	8.6*	6.4*
21	54.5	53.5	46.4*	34.2*

*p<0.03

F1 Developmental landmarks (days of occurrence; males + females combined)

	0 mkd	20 mkd	100 mkd	225 mkd
pinnae detachment	2.0	2.5	2.8	3.7*
eye opening	14.5	14.5	15.2	16.1*

*p<0.02

F1

No. Litters: 24; 22, 24, 20 (0; L, M, HD)

External and Visceral Findings: no malformations drug-related

Visceral variations:

Kidney dilated pelvis 1 3 1 5 litters

Kidney reduced papilla 0 0 0 1 "

Rotorod Performance

Time on Rotorod (seconds; *p<0.05; mean±SE)

Males: 19.7±3.82 12.1±1.49 17.6±2.69 11.6±2.45

Females: 19.7±3.06 17.2±2.55 12.5±1.93* 9.3±2.37*

Acoustic Startle (maximum response, with movement converted to millivolts, recorded following an acoustic startle stimulus)

Pre maximum input voltage (mean±SE; p<0.05 trend test)

Males: 315±78 232±70 257±71 146±64

Females: 406±66 190±56 318±68 77±13*

Pre average voltage

Males: 34±8 21±8 30±9 15±7

Females 39±7 18±6 31±8 5±1

PERINATAL-POSTNATAL STUDY IN RATS (0, 20, 100, or 225 mg/kg/day)

F1 body weight in grams ($p<0.03$):

week 3:	58	58	50*	42* (M)		54	53	46*	33* (F)
week 13:	525	538	511	493* (M)		306	305	294	280* (F)

Survival (%) postnatal weeks 3-13

Males:	96	100	100	100
Females:	100	100	100	88*

Gross Pathology (F1):
no drug-related findings in 48, 42, 46, 14 pups (Male) and 47, 43, 46, 16 pups (Female)

F1 Females gestation weight and food consumption: no drug effects but n= 19, 17, 20, 6

Maternal F1 term sacrifice parameters: no effects on corpora lutea, implantations, live/dead fetuses, litter size but HD is only 6 females and high variability in all parameters

F2 Fetal Term Sacrifice: no effects on survival to term, body weight, sex ratio, or placental weight but same problem as above (n=48, 42, 46, 6 females in 0, L, M, & HD).

ORAL FERTILITY/EARLY EMBRYONIC DEVELOPMENT IN FEMALE RATS

RR 745-02295. April 1994. Parke-Davis.

TREATMENT: Four groups of female Sprague-Dawley rats (**25/g** plus 5/g for plasma drug levels) received **0, 20, 100, or 225 mg/kg** daily by gavage in 0.5% methylcellulose for 15 days prior to mating with untreated males, throughout mating and continuing until gestation day 7. Females were sacrificed on gestation days 13-15 and reproductive parameters evaluated.

RESULTS

MORTALITY: one HD (relationship to tx "equivocal")
CLINICAL SIGNS (HD): alopecia (9/25), sporadic salivation
BODY WEIGHT GAIN: no significant differences pre-mating; decrease gestation days 1-7 (HD)

FOOD CONSUMPTION: decreased 10% HD (first week of premating) and increased days 6-15 of mating and days 8-13 of gestation

GROSS PATHOLOGY: Alopecia in 9 HD
ESTROUS CYCLES: no apparent effects but no statistical analyses were conducted
REPRODUCTIVE PARAMETERS: no effects (including pre- implantation loss, corpora lutea, live or dead fetuses, resorptions)

postimplantation loss:	7.0±1.8	7.9±1.5	7.2±1.4	13±4.1

($p>0.019$)

ORAL FERTILITY/EARLY EMBRYONIC DEVELOPMENT IN MALE RATS

RR 745-02298. April 1994. Parke-Davis.

TREATMENT: Five groups of male Sprague-Dawley rats (30/g) received **0, 20, 100, or 175 mg/kg** daily by gavage in 0.5% methylcellulose for 11 weeks prior to mating with untreated females, throughout mating (a maximum of 19 days) and continuing until necropsy during treatment week 17. A separate group was untreated. Blood for plasma concentrations was collected drug week 15 from 5 males in each group predose and 1, 2, 8, 12, and 24 hours postdose; controls only once two hours postdose.

RESULTS

MORTALITY: three (0, 20, 175 mkd; attributed to gavage error)

CLINICAL SIGNS: skin abnormal color in 1, 1; 2, 2, 5

BODY WEIGHT GAIN: decreased MD (17%) and HD (25%) premating

FOOD CONSUMPTION: decreased MD (7%) first 2 weeks and HD (5-16%) first 4 weeks

REPRODUCTIVE PARAMETERS (males):

No effects on days to mating, copulation index, fertility index

REPRODUCTIVE PARAMETERS (females):

No effects on preimplantation loss; no. with viable litters, live/dead fetuses, resorptions

Postimplantation loss: 5.8 ±1.1; 6.8±1.7 7.1±1.1 7.2±1.6 9.0±1.7 (mean±SE)

ORGAN WEIGHT (testis): 0.63 (untreated), 0.64 (vehicle), 0.64, 0.65, 0.72* ($p<0.02$ trend)

GROSS PATHOLOGY (males): no drug-related findings

HISTOPATHOLOGY (testis & epididymis): "no remarkable findings"

SECRETION OF RADIOACTIVITY IN MILK

RR 764-02360. March 1995. Parke-Davis

TREATMENT: Nine lactating rats were given a **single 10 mg/kg dose** (48 uCi) of [^{14}C]CI-981 in 0.5% methylcellulose. Six hours postdose, plasma and livers of nursing pups as well as milk, plasma, and livers of the dams were analyzed for radioactivity.

Dams			**Pups**	
Liver	Plasma	Milk	Plasma	Liver
9 ug/g	0.1 ug/ml	0.1 ug/ml	0.05	0.04

PLACENTAL TRANSFER OF RADIOACTIVITY

RR 764-02344. March 1995. Parke-Davis

TREATMENT: Six pregnant (gestation day 19) rats were given a **single 10 mg/kg dose** (62 uCi) of [^{14}C]CI-981 in 0.5% methylcellulose. Six hours postdose, rats were killed and carcass and livers of fetuses were analyzed for radioactivity as well as plasma, placenta, and livers of the dams .

Dams			**Pups**	
Liver	Plasma	Placenta	Fetus	Liver
27 ug/g	0.18 ug/ml	0.11 ug/g	0.035 ug/g	0.18 ug/g

"[^{14}C]CI-981 and/or its metabolites undergo placental transfer in pregnant rats." p.5

SPECIAL STUDIES

RR 741-00043 DIFFERENTIAL PARTITIONING INTO MODEL MEMBRANES

(vol 1.31) 740-02868

"Rapidly equilibrated within 5 minutes"; "has the potential to rapidly transport across membrane barriers..." This includes the ortho and para metabolites.

RR 740-02868: COMPARISON OF INHIBITORY ACTIVITY OF STATINS

	IC50 (nM)
Pravastatin	40
Lovastatin	13
Fluvastatin	12
Atorvastatin	7

RR 740-02778: CARDIOVASCULAR EFFECTS IN RATS

No effects on blood pressure and heart rate in conscious, normotensive rats (four days of ascending oral doses of 1, 3, 10, and 30 mg/kg).

RR 740-02884: CARDIOVASCULAR EFFECTS IN DOGS

A single, oral 100 mg/kg dose to three conscious mongrel dogs did not affect heart rate or blood pressure over 4 hours.

SUMMARY AND EVALUATION: Atorvastatin (CI-981) is the fifth HMG CoA reductase inhibitor submitted as an NDA to the FDA. Four are marketed: lovastatin and simvastatin (Merck), pravastatin (Bristol-Myers Squibb), and fluvastatin (Sandoz). The drugs function by inhibiting the enzyme HMG CoA reductase, a key early regulatory step in cholesterol synthesis.

The review of this statin has been complicated by two changes during development: **1) the assay** for drug in biological tissues was changed from
in 1993 and **2)** the form of the drug was changed from **amorphous to crystalline** in 1995, at the end of development. In fact, with the exception of 13-week comparative (crystalline vs amorphous form) studies in rats, mice, and dogs in July 1995, all preclinical studies were done with the amorphous form. These studies include the 2-year dog, 1-year rat, 2-year carcinogenicity studies in mouse and rat, reproductive toxicity, genotoxicity, and ADME studies.

COMPARISON OF AMORPHOUS AND CRYSTALLINE FORMS OF DRUG
There were a few differences in toxicity in the comparative rat and mouse studies between the two forms: the **epididymis** was an additional target organ with the crystalline form in rats while there was increased **bone marrow toxicity** and **necrosis of the medullary sinus lymph node** with the crystalline form in mice. However, the dog has been the best model for humans in terms of metabolism, pharmacodynamic effects, and toxicity for this class of drugs, and thus, we give more weight to what is seen in dog studies. And it was in the dog study that the most dramatic difference between the two drug forms was seen.

DOGS THAT DIED (13-week comparison study):
The findings in the 13- week dog study comparing the crystalline and amorphous forms has provided cause for concern: there was mortality at both 40 and 120 mg/kg in dogs given the crystalline form after only 3 months treatment, while there was no mortality at any dose in dogs given up to 120 mg/kg of the amorphous form. We do not know if 40 mg/kg is the lowest effect level for mortality with the crystalline form or whether a lower dose also might have been lethal had the study continued for one year (the normal treatment period for the dog study).

CAUSE OF DEATH (crystalline form): The dogs died from hemorrhaging (intestinal tract, gallbladder, adrenal gland, lung) along with muscle degeneration (masseter, psoas, diaphragm, and tongue) and bone marrow changes (decrease of maturing erythroid and increase of maturing myeloid).

DOG MUSCLES (affected by drug):

Masseter:	Raises mandible, closes jaws
Psoas major:	Flexes trunk; flexes and rotates thigh medially
Psoas minor:	Flexes trunk on pelvis
Tongue and diaphragm	

Muscle degeneration is a class finding for statins but occurred in the 13-week study in all the muscles examined: tongue, diaphragm, masseter, and psoas muscles (the masseter muscle was added to the list of tissues to be examined after the study began due to clinical signs of oral pain). The **10 mg/kg dose was the no effect dose for muscle degeneration (crystalline form) whereas there was no muscle degeneration up to 120 mg/kg (amorphous form) in this study.**

A comparison of the dog toxicity data obtained in the 13-week crystalline vs amorphous comparison study with data obtained from earlier studies is complicated by the use of 3-year old dogs (one normally would use 6-month old animals). Thus, there remain two major unknowns with the crystalline form: what would happen in a longer study (than 3 months) and what would one have seen had younger dogs been used.

DOGS THAT LIVED (13-week comparison study)
Amorphous form: minimal/mild congestion of gallbladder and bile duct hyperplasia (at 40 mg/kg and above) as well as a decrease in proliferating erythroid at 120 mg/kg. The gross pathology report noted red discoloration of the large intestinal mucosa in all females at 120 mg/kg.

Crystalline form: There were effects on bone marrow: increase in maturing myeloid and decrease in maturing erythroid (although not significant at $p<0.01$) as well as degeneration of the psoas muscle at 40 mg/kg. The gross pathology report noted red discoloration of the large intestinal mucosa in females at 10 mg/kg and above.

The sponsor stated (vol 1.58, p. 24) that "High doses of the crystalline (form) resulted in more severe clinical signs, moribundity, mortality, and changes in body weight, food consumption, hematology, clinical biochemistry, and pathology than did the amorphous form. *However, identical findings have been reported in previous studies in dogs administered amorphous CI-981.*" This is not quite accurate (see below).

It is true that in the **2-year oral toxicity study in dogs with the amorphous form** there were deaths in two males at 120 mkd (weeks 7 and 9) with toxicity seen in the liver (fibrosis), adrenal (hemorrhage), gallbladder (mucosal degeneration/necrosis), tongue (myocyte degeneration), and intestines (mucosal hemorrhage). Thus, at toxic levels of the amorphous form, there was overlap of some target organs. However, there were differences as well: the tongue was the only muscle showing degeneration in the 2-year study whereas in the **3-month study with the crystalline form**, the **psoas, masseter, and diaphragm** were targets as well as the tongue. *In addition, the sponsor stated that in the 2-year dog study, "Toxicity in females occurred only at 120 mkd and was less severe than seen in males at that dose."* This is the *opposite* of what occurred in the 13-week dog study with the crystalline form: deaths occurred more frequently in females (*3/3* females at 120 mkd and 1/3 females at 40 mkd vs only 2/3 males at 120 mkd).

MORTALITY IN DOGS

	Crystalline (13-wk study)		**Amorphous** (13-wk study)	
Dose	Males	Females	Males	Females
40 mkd	**0/3**	**1/3**	**0/3**	**0/3**
120 mkd	**2/3**	**3/3**	**0/3**	**0/3**

There were "higher plasma concentrations in animals receiving the crystalline form of CI-981 compared to the amorphous form." "... the severe toxicity observed in animals given the crystalline form ...can be related to increased systemic exposure" (p.240). This may be true but 50% higher plasma concentrations were also seen in people given the crystalline form of the drug.

OTHER FINDINGS IN DOGS (amorphous form)
MAJOR STUDIES:
1) ESCALATING dose study starting at 80 mg/kg for 2 weeks followed by 20 mkd increases weekly for 8 weeks and 40 mkd increases up to 320 mkd (2/s; one male died at 180 mkd and one female died at 280 mkd; study terminated at 320 mkd (RR 745-01873)
2) 3-MONTH with doses of 0, 10, 40, 80 mkd (160 mkd not tolerated) (RR 745-01594)
3) TWO YEAR with doses of 0, 10, 40, 120 mkd (RR745-02334)

DOG BRAIN

There was *hemorrhage, necrosis of the neuropil, neutrophilic infiltrates* of basal nuclei associated with *fibrinoid vascular necrosis, and perivascular hemorrhage as well as multifocal vacuolation in optic nerve* (findings in one moribund female at 280 mkd in the escalating dose study). *Tonic convulsions* were seen in one male at 10 and one at 120 mkd (the 2-yr study). The Parke-Davis pathologist noted *edema and hemorrhage* in the choroid plexus of a female sacrificed moribund at 120 mg/kg in the 3-month study.

Hemorrhaging in the brain has been a class finding with the statins (with atorvastatin, gi hemorrhaging was usually the cause of death). However, one person given 120 mg (amorphous) suffered mental symptoms (see below) that along with the above dog findings, implies that this drug shares, to some degree, the CNS toxicity seen with the other statins. The brain is exposed to drug: 5% of the plasma drug level was present in dog brain (dosing radioactive atorvastatin) and in vitro studies showed more facile crossing of membrane barriers than the other statins (p. 52 of review).

DOG TOXICITY amorphous form (continued)

GI TRACT (dogs; amorphous form)

Red feces at ≥100 mkd; Severe bloody diarrhea in one male at 180 mkd; gastric mucosal erosions and villous atrophy, hyalinization of lamina propria, erosion of small intestine; large intestine also plus congestion (Escalating dose study).

Red feces at ≥40 mkd (males) and 120 mkd (females) at one and two years (2-yr study)

Mucosal hemorrhage (large intestine); necrosis and congestion and blunting of villi of small intestine (2-yr study)

Granulomas in the livers of dogs treated for one year at 120 mg/kg/day (2-yr study) were thought to be due either to compromised integrity of the gi tract or hepatocyte necrosis (Dr. Scott Eustis, consultant to FDA from National Institute of Environmental Health Sciences (Review of November 4, 1993).

Red feces at≥40 mkd (females) and 120 mkd (males) & hemorrhage of intest. tract (3-month study)

LIVER (dogs; amorphous form)

Hepatocellular basophilia (180 mkd); degeneration with atrophy and hyperplasia of Kupffer cells (Escalating dose study)

Atrophy, pigmentation, vacuolation, lipidosis (3-month study)

Bile stasis, fibrosis central vein (2-yr study)

PANCREAS

Acinar atrophy (Escalating dose study)

BONE MARROW

Elevated myeloid:erythroid ratio in all dogs (Escalating dose study)

No effects on bone marrow at $p<0.01$ (2-yr dog amorphous)

ADRENALS

Decreased fine cytoplasmic vacuolation of z.fasciculata all dogs (Escalating dose study)

MUSCLE

Opening of the dog jaw was painful with degeneration, necrosis and regeneration of muscle cells with decrease of fat cells in tongue. (Escalating dose study)

Degeneration and regeneration muscle cells in tongue (120 mkd moribund) (2-yr dog)

LENS

Decreases in lenticular glucose, K, and protein suggestive of alteration in lens hydration; loss of nonenzymatic protein; most evident in females (3-month study)

SPERM ANALYSIS (2-year dog toxicity study)
(week 50= vol.; week 64= % abnormal; wk.78= % normal)

	control	**10 mkd**	**40 mkd**	**120 mkd**
Sperm volume (%)	7.0±0.95	6.7± 0.54	5.8± 0.87	5.3± 0.59
Abnormal heads (%)	5.4±2.6	2.0 ± 0.8	0.8 ± 0.6	18 ± 13
Normal heads (%)	27± 14	28 ±8.7	30± 15	16± 0.00

Findings were dose-related, but the large SE prevented significance at $p<0.05$. Other weeks lacked findings.

FINDINGS FROM RAT TOXICITY STUDIES

RAT (crystalline vs amorphous forms, 3-months at 0,10,30,100 mkd):
Testis (and epididymis for crystalline form) decreased in weight; **epididymis** was aspermatic and had aplasia (crystalline). **Liver** was a target organ for both forms (atypia, hyperplasia)

RAT (amorphous form; 3-months at 0,5,20,70,125 mkd)
Skeletal muscle (fibrosis, necrosis), **liver** (atypia, necrosis, hyperplasia), **testes** (degeneration multinucleated cell), **bone marrow** (myeloid count up, maturation index down)

RAT (amorphous form; 1-yr study at 0,5,70,125 mkd)
Liver (atypia, necrosis), **adrenal** (hyperplasia), **esophagus** (hemorrhage, necrosis not related to gavage), **cartilage** (degeneration); **CNS (tonic convulsion)**: one male and one female at 5 mkd and two males and two females at 70 mkd (seen on handling but this is probably because there were so many rats that CNS episodes could have easily been missed).

REPRODUCTIVE TOXICITY (amorphous form)

RATS: Radioactive atorvastatin **crosses the placenta** (found in placenta as well as fetal plasma and liver) and is **secreted into milk** (found in plasma and liver of pups).

RAT: **Dosing gestation day 7 through lactation** (significant findings):

Lethal to 2/30 dams @ 225 mkd

Decreased BW of F1 (males and females at birth, day 4, day 21, day 91): 225 mkd
(males and females on days 4 and 21) : 100 mkd

Decreased survival of F1 (males & females at birth, neonate, weaning): 225 mkd
(females at week 13) : 225 mkd

Decreased development of F1:

Delay of pinnae detachment and eye opening: pups of mothers treated at 225 mkd

Rotorod performance: decreased as f(dose), significant female pups at 100 mkd

Acoustic startle: decreased as f(dose), significant female pups at 225 mkd

RAT: **Dosing Females Before and Through Mating Until Gestation Day 7**:

Postimplantation loss increased at 225 mkd

RAT: **Dosing Males and Females in diet from before mating and through lactation**

Sperm analysis: Motility decreased at 75 mkd
% Abnormal increased at 75 mkd
Spermatid head concentration decreased at 75 mkd (testis)

RAT: **Dosing Males Before, Through Mating and Until Week 17**

Postimplantation loss increased as f (dose) but N.S.

RABBIT: **Dosing Gestation Days 6-18**: (0, 10, 50, 100 mkd)

Lethal to dams at 100 mkd

Preimplanation loss increased all treated (no statistics)

Postimplantation loss increased (2-fold at 50 mkd; 3-fold at 100 mkd)

Gallbladder agenesis at 100 mkd (3-fold background); tail unossified in 0, 0, 25, 50% of litters

FINDINGS FROM MOUSE TOXICITY STUDIES

MOUSE (3-months at 0,100,200,400 mkd comparison amorphous/crystalline forms):

Bone Marrow [Myeloid maturation index decreased (all treated), erythroid series increased (HD male), eosinophils decreased (HD male) (crystalline)]

Lymphocytes increased both forms (HD males)

Liver and adrenal were target organs for both forms.

Lymph node had multinucleated cells (all treated crystalline form) and necrosis (M & HD females)

OTHER MOUSE TOXICITY STUDIES

Target organs: **esophagus** (degeneration of muscle); **skeletal muscle** degeneration; **liver** (cellular alteration and anisokaryosis =unequal size nuclei); **adrenal** (atrophy x-zone, decreased fine vacuoles)

CARCINOGENICITY (Mouse; amorphous form) (Sponsor's Analysis)

Hepatocyte adenoma (p=0.001 males at 400 mkd)

Hepatocyte carcinoma (0=0.002 females at 400 mkd)

Carcinogenicity (Rat; amorphous form) (Sponsor's Analysis)

Tumor type	p-value (peto test)
lipoma of kidney	0.044
adenocarcinoma large intest.	0.044
adenocarcinoma preputial gl	0.043
myxoma of skin	0.047
thymoma (malignant)	0.047
adenoma of parathyroid*	0.031
all tumors skeletal muscle*	0.007

* females; rest in males

Rhabdosarcomas in skeletal muscle occurred with a background incidence (at Parke-Davis) in female Wistar rats of 0.3%, and thus are very rare tumors; fibrosarcomas occurred at an incidence of 1%. **"...musculoskeletal systems of Wistar rats are rarely affected by spontaneous neoplasms."*** The two sarcomas occurred here at a combined incidence of 3% with a highly significant p value. The paper by McConnell et al, ("Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies", JNCI, 76; 283-289, 1988) states that both NCI and NTP combine skeletal muscle neoplasms. Thus, it seems correct to combine the rhabdomyosarcoma and the fibrosarcoma of skeletal muscle as Parke-Davis has done.

*Spontaneous Neoplasms in Control Wistar Rats, Walsh and Poteracki, Fund Appl Tox. 22, 65-72 (1994)

GENOTOXICITY STUDIES (amorphous form)

The following tests were negative: Ames, HGPRT in Chinese hamster ovary cells, chromosomal aberrations in the Chinese hamster lung cell assay, and the in vivo mouse micronucleus.

ADME (amorphous form)

ABSORPTION: The absolute bioavailability of atorvastatin was 12% in people, 11% in dogs, and 41% in rats.

EXCRETION:

Rat (after a single dose of 28 mg/kg): Radioactive atorvastatin was excreted 64% in the bile, 28% in feces, and 2% in the urine).

Human: 91% excreted after 2 weeks; fecal was main route. There were multiple metabolites in plasma, urine, and feces.

DISTRIBUTION:

Rat (2 hours after an oral dose of 28 mg/kg; whole body sectioning and looking at film exposed for 12 weeks): Radioactive atorvastatin was located in the liver (88%), kidney (3%), and adrenal (3%). Visible radioactivity was still present 7 days postdose in the liver and kidney.

Rat (10 mg/kg dosing for 21 days; again looking at films): Radioactivity was mainly in the liver but some was present in the adrenal, kidney, thyroid, preputial gland, spleen, bone marrow, salivary gland, and bone marrow. The peak was 4 hours postdose with measurable levels in the liver out to 7 (but not 14 days) days postdose. However, radioautography is a very insensitive proceedure and does not rule out the presence of radioactivity in other tissues.

HALF-LIFE

Enzyme assay	Radioactivity
20-30 hours (Human)	63 hours
5-8 hours (Dog)	
3-6 hours (Rat)	
1-4 hours (Mouse)	

MAJOR METABOLITES:

Mouse (plasma): β-oxidized OH atorvastatin, β-oxidized atorvastatin, unsaturated β-oxidized OH- and atorvastatin

Rat (plasma): ortho-OH and β-oxidized products; Bile= o- and p-OH metabolites and the glucuronide of o-OH CI-981)

Dog (Bile): o- and p- OH metabolites and the glucuronide of o-OH CI-981

"There are no differences in [14C]CI-981 metabolic profiles generated by rat, dog, and human hepatic microsomal preparations." (p.347, vol 1.76)

Human liver and intestine were able to produce the para and ortho hydroxy derivatives of CI-981. When liver microsomal metabolism was inhibited 90% by gestodene (a mechanism based inhibitor of CYP 3A4), metabolite formation was prevented. **"Human intestine may play a role in the disposition of CI-981."**

BRAIN LEVELS: MALE RAT (RR 764-01932)

Four rats had measurable radioactivity at one time-point postdose (2@24 h; 1@48 h and one at 14 days). There were clonic and tonic-clonic convulsions is treated rats in the 1-year toxicity study, usually seen on handling.

BRAIN LEVELS: DOG (RR 764-01948)

Five percent of the plasma counts were present in the brain of a female dog (dosing for 10 days with unlabeled drug followed by one labeled dose).

SAFETY MULTIPLES AT LETHAL DOSE IN DOGS

MULTIPLES OF HUMAN DOSE (crystalline) at which dogs died

Dog mortality compared with human using enzyme inhibition assay

	Dog (40 mg/kg/day) (6 or 7 weeks)	**Human (80 mg/day)** (8 days)	**Ratio** (dog: human)
Cmax (ng eq/ml)	1,900	140	14
AUC_{0-} (ng eq h/ml)	8,200	990	8

HUMAN COMPARISON WITH DOG NOEL

	Cmax (ng/ml)	AUC (ng h/ml)
DOG (NOEL) 10 mg/kg/day	140	480
HUMAN 80 mg/day	140	990
Ratio (Dog/Man)	1x	0.5x

The **multiples of exposure (dogs vs man) are very small** given that we are concerned with mortality and that there is **tremendous variability of plasma exposure** with this class of drug in both dogs and man (Cmax varied 15-fold and AUC 8-fold in dogs at the 40 mg/kg dose; Cmax varied 5-fold and AUC 4-fold in man at the 80 mg crystalline dose). The placebo-controlled data base for safety with the 80 mg crystalline form is 12 people dosed for 6 weeks (a 1-year comparison of 80 mg crystalline vs 80 mg amorphous form was submitted 10/16/96).

The kinetics are not linear: 80 mg increases more than dose proportionally and there are long-lived pharmacodynamically inactive metabolites (t1/2 of 63 hours in man).

The sponsor has stated that *amorphous* atorvastatin was "well tolerated at doses up to 80 mg, while transient restlessness, euphoria, mental confusion, and memory impairment were seen in a subject who received 120 mg" (vol.1.75, p.61). This patient had higher plasma levels than those without symptoms. The sponsor stated when this was first seen that "there is dose-limiting CNS toxicity" Thus, there is a clear acknowledgement, even in the sponsor's own mind, that they are close to a limit at 80 mg with the amorphous form. With the increased bioavailability of the crystalline form, where is that limit now? Ignored in the labeling are the further **effects on plasma exposure as a result of food** (food decreases absorption 25%), **age** (elderly have 43% higher levels than young), **sex** (females 18% higher than males), and **time of day** (A.M. 30 % higher than P.M.).

The 120 mg dose is 50% higher than the 80 mg dose (and the sponsor thought 120 mg amorphous dose was too high). Yet, the Cmax for the crystalline form is 50% higher than the amorphous form meaning that the 80 mg crystalline form will get us to the same potential plasma exposure that was previously cause for concern by the sponsor.

RECOMMENDATION: Because of the unknown potential for human toxicity, the relatively small margin of safety of the crystalline form of drug (8-fold based on AUC for mortality in dogs, our best animal model), and variability of plasma exposures in people, Pharmacology cannot recommend approval of the 80 mg dose. There appears to be an adequate margin of safety for the lower doses.

Clinical Pharmacology & Biopharmaceutics Review

NDA: 20-702

SUBMISSION DATE: November 5, 1996
November 6, 1996

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: Original NDA (NME) **Code:** 1P

SYNOPSIS:

Parke-Davis submitted additional documents on November 5 and November 6, 1996 to the agency after the formal review of NDA 20-702. These documents were in response to telephone conversations between the reviewer and Mr. Byron Scott, Director Worldwide Regulatory Affairs, Parke-Davis. These submissions included partial information from two study reports (Research Report 764-02589 and Research Report 764-02590). The contents of these reports pertain to the development of a dissolution specification for atorvastatin.

Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics
11/21/96

Michael Fossler for

RD initialed by Hae-Young Ahn, Ph.D., Team leader 11/21/96

Clinical Pharmacology and Biopharmaceutics Briefing (10/22/96, Huang, Strong, Fleischer, Ahn, Mehta, Shore, Chen)

MICHAEL FOSTER FOR

FT initialed by Hae-Young Ahn, Ph.D., Team leader 11/21/96

NDA 20-702 (1 copy), HFD-510(Orloff, RheeJ), HFD-340 (Vishwanathan), HFD-850 (Lesko), HFD-870(Ahn, Jones and M. Chen), HFD-870(Drug file, Chron. file, Reviewer).

OCT 25 1996

Clinical Pharmacology & Biopharmaceutics Review

NDA: 20-702

SUBMISSION DATE: June 17, 1996
October 8, 1996
October 9, 1996

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: **Original NDA (NME)** **Code: 1P**

SYNOPSIS:

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

The NDA submission includes 31 clinical pharmacology studies conducted to assess the safety, tolerance, pharmacokinetic and/or pharmacodynamic properties of atorvastatin in healthy adults, renally and hepatically impaired patients, and patients with hypercholesterolemia. Full pharmacokinetic profiles were determined in 29 clinical pharmacology studies and blood samples were collected 8 to 16 hours postdose in 2 clinical pharmacology studies. Pharmacodynamics were also evaluated in 9 of the 29 clinical PK studies.

Atorvastatin exists as multiple amorphous and crystalline forms and is a highly variable drug with percent relative standard deviation (%RSD) of approximately 50%. Intrasubject variability accounts for 66.1% of the variability in C_{max}, and intersubject variability accounts for 75.4% of the variability in $AUC_{(0-\infty)}$. Most of the clinical pharmacology studies have been conducted with tablets prepared from the amorphous bulk drug substance. The to-be-marketed/market-image

formulation is the crystalline form which is considered more stable.

Ir. vitro testing of atorvastatin indicates that aqueous solubility is pH dependent with low solubility under acidic conditions. The company proposes a dissolution method using

Bioequivalence studies show that the rate is significantly higher in the crystalline form. However, the two drug substances are similar for the extent of absorption. Both the 10 and 40 mg tablets show t_{max} and C_{max} values 2-fold shorter and 50% higher, respectively, in the crystalline form compared to the amorphous form. Bioequivalence was established between the Freiburg and Lititz manufacturing sites for the market-image crystalline form of the drug.

Atorvastatin reaches C_{max} rapidly (within 1 to 2 hours) and steady state is achieved in 3 days. The absolute bioavailability is ~12% and the systemic availability of HMG-CoA reductase inhibitory activity is ~30%. Volume of distribution is 565 liters and atorvastatin is $\geq$ 98% bound to plasma proteins. The majority of the dose, 98.4% is excreted in the feces with 1.23% found in the urine. The drug does not appear to undergo enterohepatic recirculation. Plasma half-life of atorvastatin is ~14 hours, atorvastatin equivalents 23 hours, and inhibitor activity half-life 20 to 30 hours. No dose dependence in half-life occurs. Mean accumulation ratios over the dosing interval as calculated using AUC data are 1.6 following once daily and 3.3 following twice daily administration.

Atorvastatin is extensively metabolized in the liver and intestines to ortho- and parahydroxylated metabolites in addition to several beta-oxidation products. The ortho- and parahydroxylated products are pharmacologically active. In vitro studies indicate atorvastatin is metabolized by CYP3A4. It is a chiral compound with 5R,3S and 5S,3R-diastereoisomers and 5S,3S-enantiomers. It does not isomerize into the various diastereoisomers. Seventy percent of inhibitory activity is due to the active metabolites and the ability to inhibit the enzyme between parent drug and metabolites is similar. A 10-fold difference in formation of metabolites occurs between the two metabolites with M2 (the orthohydroxy metabolite) forming much faster. Plasma radioactivity ($t_{1/2}$=62.5 hr) is detected longer than atorvastatin concentrations ($t_{1/2}$=12.6 hr) suggesting the presence of long-lived metabolites that are not pharmacologically active. Gestodene and ethinyl estradiol, 3A4 metabolized inhibitors, inhibit metabolism of atorvastatin 90% and 60% respectively, thereby confirming atorvastatin as a 3A4 drug. The disposition of the metabolites and the binding capacity have not been elucidated. Most of the studies quantitated or expressed the activity as atorvastatin equivalents (parent drug and metabolites).

Dose proportionality studies and food effect studies previously conducted with the amorphous form are repeated with the crystalline form. The kinetics of atorvastatin are not linear over the range of 10-80 mg for C_{max} and C_{min}. However, AUC is dose proportional for both forms of the drug substance. At the 80 mg level , C_{max} increases more than proportionally with increasing dose and C_{min} increases less than dose proportionally. This was seen in both the amorphous and

crystalline forms. Food decreases C_{max} and AUC by 25% and 9%, respectively, and time of administration also impacts plasma concentrations with a 30% decrease in C_{max} and AUC in the evening. Food and diurnal variations do not affect LDL-C reduction.

Special population studies to evaluate the effect of age, gender, and renal and hepatic insufficiency indicate the following: C_{max} and AUC are 40% and 30%, higher, respectively, in the elderly with no impact on LDL-C reduction, and C_{max} is 20% higher and AUC is 10% lower in females with no impact on LDL-C reduction. Renal insufficiency has no effect on plasma concentrations or LDL-C reduction. However, hepatic insufficiency causes a significant increase in C_{max} 16-fold and 11-fold in AUC.

Drug interaction studies have been conducted using the following compounds: antipyrine, erythromycin, ethinyl estradiol and norethindrone(Ortho-Novum 1/35), cimetidine, digoxin, warfarin, antacids (Maalox®) and colestipol. Atorvastatin has no effect on the pharmacokinetics of antipyrine, warfarin and cimetidine. Coadministration of atorvastatin and digoxin causes a 20% increase in steady-state digoxin plasma concentration and a 15% increase in $AUC_{(0-24)}$. The presence of atorvastatin increases mean steady-state ethinyl estradiol and norethindrone C_{max} values by 25-30% and $AUC_{(0-24)}$ 20-30%. Contraceptive failure due to drug-drug interaction is not a concern, however this increase in ethinyl estradiol should be considered when selecting a contraceptive dose. In patients receiving Maalox® a 34% decrease in both atorvastatin equivalent C_{max} and $AUC_{(0-24)}$ is observed. However, LDL-C reduction is not affected. Coadministration of atorvastatin and erythromycin results in higher atorvastatin C_{max} and $AUC_{(0-)}$ 38% and 33% respectively. Coadministration of atorvastatin with colestipol reduces the 8-16-hour postdose atorvastatin concentration by ~26%, however LDL-C reduction is greater when the two drugs are administered together.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed NDA 20-702 submitted on June 17, 1996 and it has found the NDA adequate to support the human pharmacokinetic section of clinical pharmacology. The to-be-marketed formulation and the clinical trial formulation are not bioequivalent. The safety of this drug should be determined by the reviewing medical officer especially at the higher dose (80 mg). Recommendations and comments to be sent to the sponsors (p. 37) and labeling comments (p. 38) should be sent to the sponsor as appropriate.

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BACKGROUND:

Cardiovascular diseases have been the leading cause of death in the United States for many years. Many studies have linked a reduction in low-density lipoprotein cholesterol (LDL-C) to a reduction in cardiovascular events. Hypercholesterolemia is treated with dietary restriction, addition of an anion-exchange resin, a nicotinic acid compound or a HMG-CoA reductase inhibitor. HMG-CoA reductase inhibitors are believed to be the most effective cholesterol lowering agents typically lowering LDL-C up to 40%, total cholesterol up to 29%, triglycerides 12 to 15% and HDL-C 6 to 10%. The sponsor believes that the greater efficacy in lowering both LDL-C and triglycerides, and the safety profile of atorvastatin warranted a 1P rating which the agency granted. Atorvastatin is being touted as the first effective drug therapy for patients with familial hypercholesterolemia who are refractory to conventional cholesterol therapy.

Atorvastatin is an anhydrous calcium salt $(C_{33}H_{34}FN_2O_5)Ca$ M.W. 1155.38. It is a white to off-white solid with a pKa of 4.6 and partition coefficients, log P of 3.66, 3.18 and 1.42 at low pH, pH 4.0 and pH 7.4, respectively. The final drug product will be made from a crystalline material and provided as elliptical film-coated tablets in 10, 20 and 40 mg strengths. The sponsor abandoned efforts to manufacture the amorphous form of the drug because the final product contained large levels of residual solvent which required extended drying and led to degradation of the product.

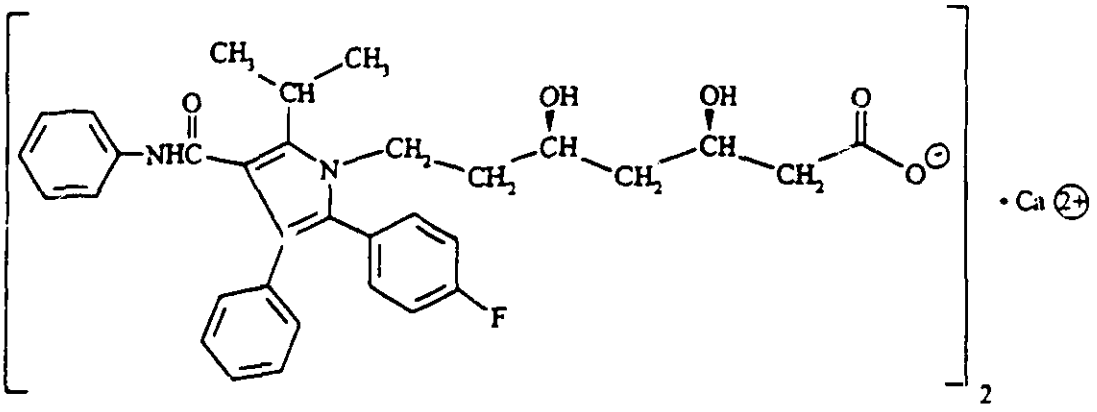


Figure 1: The chemical structure of atorvastatin (LIPITOR®)

Serial blood samples for PK profiles were obtained from 601 healthy adults including 24 subjects with LDL-C levels between 160 and 250 mg/dL. Four hundred and forty-four (444) patients with hyperlipidemia gave blood samples 8-16 hours postdose. Males accounted for 58% of subjects. The ethnicity of the subjects is as follows: 90% of subjects Caucasian, 7% Black, 0.3% Asian and 2.8% other.

Protocol Number	Title	Page
981-030-0	An absolute bioavailability study of atorvastatin (RR 744-00265, Mar 28, 1996)	14
981-090-0	A single-dose bioavailability study comparing 10-mg atorvastatin tablets prepared from crystalline I lot to 10-mg atorvastatin tablets (amorphous B) used in protocol 981-008 (RR 744-00208, Sep 7, 1995)	15
981-111	A single-dose bioequivalence study comparing 10-mg market-image atorvastatin tablets prepared from a crystalline 1 bulk drug lot to 10-mg atorvastatin tablets from a lot used in Protocol 981-008 relative to a stable-isotope-labeled internal standard (RR 744-00232, Mar 25, 1996)	15
981-112	Single-dose bioequivalence study comparing 40-mg market-image and non-market-image atorvastatin tablets prepared from crystalline 1 bulk drug lots to 40-mg atorvastatin tablets from a lot used in clinical trials relative to a stable-isotope-labeled internal standard (RR 744-00256, Apr 8, 1996)	16

981-142	A single-dose bioequivalence study comparing 10-mg market-image tablets manufactured in Freiburg to 10-mg market-image tablets manufactured in Lititz (RR 744-00260, Apr 18, 1996)	17
981-143	A single-dose bioequivalence study comparing 40-mg market-image atorvastatin tablets manufactured in Freiburg to 40-mg market-image atorvastatin tablets manufactured in Lititz (RR 744-00268, Apr 18, 1996)	17
981-003	Effect of food on the bioavailability of CI-981 capsules in healthy volunteers (RR 744-00139, Sep 13, 1993)	17
981-098-0	A study in healthy volunteers of the pharmacologic activity and pharmacokinetics of atorvastatin tablets prepared from a crystalline 1 lot as a function of dosing with or after evening meals (RR 744-00241, Mar 7, 1996)	18
981-031-0	A study in healthy volunteers of the pharmacologic activity and pharmacokinetic profiles of atorvastatin (tablets) as a function of dosing with or after evening meals (RR 744-00207, Sep 7, 1995)	18
981-017-0	An open-label, randomized, multiple-dose, 2 way crossover study of the pharmacologic and pharmacokinetic profiles of oral CI-981 (tablets) as a function of morning-versus-evening dosing in healthy subjects (RR 744-00115, Sep 27, 1993)	19
981-019-0	Intrasubject and intersubject variability of CI-981 pharmacokinetic characteristics in healthy volunteers (RR 744-00138, Oct 18, 1993)	19
981-078-0	A study utilizing a stable isotope technique to provide information for the design of pivotal atorvastatin tablet bioequivalence studies (RR 744-00243, Apr 3, 1996)	20
981-020-0	A study of the mass balance and metabolism of [^{14}C] CI-981 following multiple-dose CI-981 administration in healthy volunteers (RR 744-00163, June 5, 1994)	22
	Atorvastatin metabolism in isolated human hepatocytes (RR-MEMO 764-02556, Feb 16, 1996)	22
	In vitro human microsomal metabolism of CI-981 (RR 764-02313, Mar 11, 1995)	23
	Comparison of in vitro HMG-CoA reductase inhibition activities of atorvastatin, atorvastatin metabolites, and analogs in human plasma (RR 764-02573, Mar 29, 1996)	23

	Metabolite identification in bile fistula rats following a single oral 10-mg/kg suspension dose of a mixture of [d_5]/[d_0] CI-981 and [^{14}C] CI-981 (RR-MEMO 764-02216, Sep 30, 1994)	23
	Identification of CI-981 metabolites in dog bile following a single oral 10 mg/kg suspension dose of a mixture of [d_5/d_0] CI-981 and [^{14}C] CI-981 (RR 764-02256, Oct 5, 1995)	23
	Characterization of the inhibitory profile of Parke-Davis compound, CI-981, toward isoforms of human cytochrome P450 (RR 764-02546, Apr 9, 1996)	23
	Assessment of in vivo isomerization of atorvastatin (5R, 3R diastereoisomer) to PD 145748 in atorvastatin-treated mice, rats, dogs, and humans (RR-MEMO 764-02534, Feb 28, 1996)	23
981-99	A multiple-dose, dose proportionality study of atorvastatin tablets prepared from crystalline 1 lots (RR 744-00247, Mar 28, 1996)	23
981-006	A multiple-dose study to evaluate the pharmacokinetic-pharmacodynamic relationship and dose proportionality of atorvastatin (CI-981) in subjects with raised cholesterol levels (RR 744-00215, Mar 29, 1996)	24
981-059	An oral, multiple-dose, safety, tolerance, pharmacokinetic, and pharmacodynamic study of atorvastatin (CI-981) tablets in subjects with various degrees of renal function (RR 744-00204, Apr 15, 1996)	27
981-60	An oral, multiple-dose safety, tolerance, pharmacokinetic, and pharmacodynamic study of atorvastatin (CI-981) tablets in healthy volunteers and patients with hepatic impairment (RR 744-00222 Mar 7, 1996)	27
981-045	The effect of age on CI-981 single-dose pharmacokinetics in healthy volunteers (RR 744-00167, Jul 12, 1994)	27
981-32	A study of the effects of atorvastatin on hepatic oxidative drug metabolism as measured by antipyrine clearance in healthy volunteers (RR 744-00180, Jul 12, 1995)	28
981-033	An open-label, multiple-dose, randomized, 2 way crossover study to evaluate the effects of cimetidine on the steady-state pharmacokinetics and pharmacodynamics of atorvastatin (CI-981) in healthy subjects (RR 744-00210, Jan 18, 1996)	28

981-34	A study to evaluate the effects of atorvastatin (CI-981) on the steady-state pharmacokinetics of digoxin in healthy volunteers (RR 744-00201, Apr 1, 1996)	29
981-35	A study to evaluate the effects of Maalox® TC on the steady-state pharmacokinetics and pharmacodynamics of atorvastatin in healthy volunteers (RR 744-00202, Jan 16, 1996)	29
981-036-0	A study to determine the effect of multiple-dose atorvastatin (CI-981) administration on prothrombin time in patients maintained on warfarin (RR 744-00227, Apr 1, 1996)	29
981-66	A study to determine the effects of atorvastatin (CI-981) on the pharmacokinetics of an oral contraceptive agent (Ortho-Novum® 1/35) (RR 744-00229, Mar 22, 1996)	29
981-109	A study to evaluate the effects of erythromycin on the pharmacokinetics of atorvastatin (RR 744-00262, Mar 15, 1996)	30
981-43	A 12-week, randomly-assigned, open-label multi-center study evaluating efficacy and safety of the monotherapies of atorvastatin (CI-981) and colestipol and the combination therapy of atorvastatin and colestipol in patients with hypercholesterolemia (RR 720-03361, Feb 24, 1995)	30
981-56	A 1-year randomized, open-label, parallel-arm, multi-center study to compare the safety and efficacy of 80 mg atorvastatin versus colestipol alone, and versus colestipol in combination with either 40 mg simvastatin or 40 mg atorvastatin, in patients with severe primary hypercholesterolemia (RR 720-03600, Apr 4, 1996)	30
	Population pharmacokinetics of atorvastatin (RR MEMO 764-02520, Apr 18, 1996)	31
981-4	A 6-week, double-blind, placebo-controlled, dose-ranging study of once daily CI-981 in patients with elevated low-density lipoprotein cholesterol (RR 720-03113, Apr 23, 1993)	32
981-96	A multi-center, nonblind, placebo-controlled, 6-week, dose-ranging study of once daily atorvastatin in patients with elevated LDL-cholesterol (RR 720-03602, Apr 17, 1996)	36

DRUG FORMULATION:

Several formulations were used in the drug development process. Most of the clinical development studies to include the pivotal studies were performed using the amorphous form of atorvastatin. Only one clinical study (A multicenter, nonblind placebo-controlled 6 week, dose-ranging study of once daily atorvastatin in patients with elevated LDL-cholesterol--Study 981-96) which evaluated the crystalline form of the drug was included as part of the submission. The remainder of the studies which evaluated the crystalline form were pharmacokinetic studies. The to-be-marketed crystalline formulation was phased into clinical use throughout 1995 in Phase 3.

The amorphous form existed as irregularly shaped particles ranging in size from and the crystalline form exists as rod-shaped particles with aggregates of long particles ranging in size from . The amorphous form was hygroscopic and unstable when exposed to oxygen. Neither situation was a concern with the crystalline form. Atorvastatin calcium was practically insoluble in aqueous solutions at low pHs. However, the solubility between the two forms was equal.

Several formulations of atorvastatin were evaluated which included: a capsule formulation, a tablet in capsule formulation, an amorphous tablet and finally a crystalline tablet which represented the to-be-marketed formulation. For phase 2 studies, two similar powder formulas were developed. One formulation was used to 2.5, 5.0 and 10 mg strength tablets, while a second formula was used for 20 and 40 mg tablet strengths, as well as an investigational strength which was never used clinically. Initial Phase 3 clinical investigations for 5-40 mg tablets used the same powder blend as the low dosage Phase 2 tablets (See Table 1). Three strengths, 10 20 and 40 mg tablets were identified for commercial development. The composition of these tablets were the same as Phase 3, except the color of the film coating was changed from yellow to white and the drug substance was changed from amorphous to crystalline. The clinical trial formulations were nondebossed tablets while the market-image tablet was debossed.

TABLE 1. Percent Composition of Atorvastatin Phase 2, Phase 3 and Commercial Tablet Formulations

	Formula Percent		
Components	Phase 2 2.5-10 mg Phase 3 5-40 mg (Pivotal)	Phase 2 20-80 mg	Market Image 5-40 mg
Atorvastatin Calcium, Amorphous OR Atorvastatin Calcium Crystalline Calcium Carbonate, USP (Heavy) Microcrystalline Cellulose, NF Lactose, NF, Hydrous[a] Croscarmellose Sodium, NF Polysorbate 80, NF Hydroxylpropyl Cellulose, NF Purified Water, USP[b] Magnesium Stearate, NF	6.91	20.72	----

[a] Adjusted based on the actual quantity of atorvastatin calcium required.
[b] Does not appear in the final product.
The 10 mg, 20mg and 40 mg formulations are proportional.

The dissolution of atorvastatin calcium tablets was evaluated in the following media:

Bioequivalence studies were conducted in tablets made from both the amorphous and crystalline drug substances that were manufactured at the Morris Plains, Lititz and Freiburg facilities. Both the Lititz, PA and Freiburg, Germany sites will manufacture the commercial formulation. Aqueous solubility of atorvastatin was pH dependent with low solubility under acidic conditions (pH<4). In phosphate buffer solubility increased to approximately 0.7 mg/ml. The solubility in the various dissolution media is as described in

Table 2.

TABLE 2. The Solubility of Atorvastatin Calcium in Various Aqueous Media	
Medium	**Solubility (mg/ml)**
0.1 N Hydrochloric Acid	0.02
Purified Water	0.27
0.05 M Acetate Buffer, pH 4.5	0.07
0.05 M Phosphate Buffer, pH 7.4	0.72
0.5 % SLS	2.80

The proposed dissolution method is

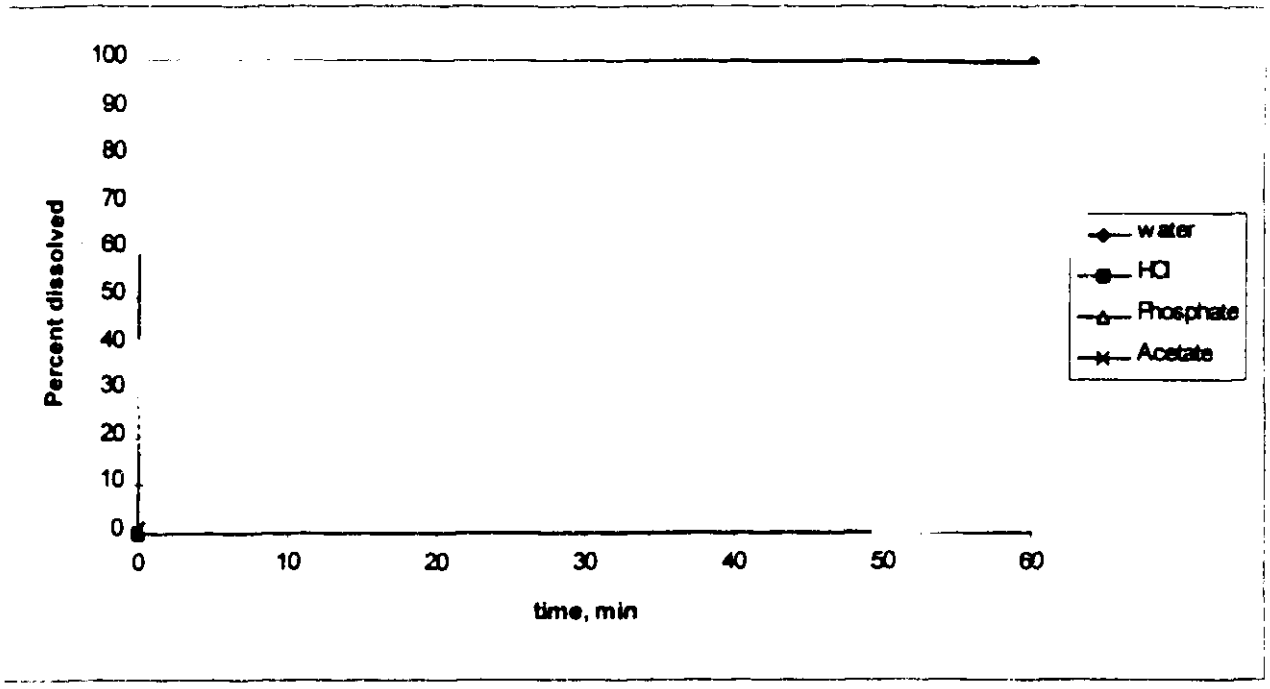


Figure 2: Comparison of atorvastatin dissolution profiles in four different media using the 40 mg dosage

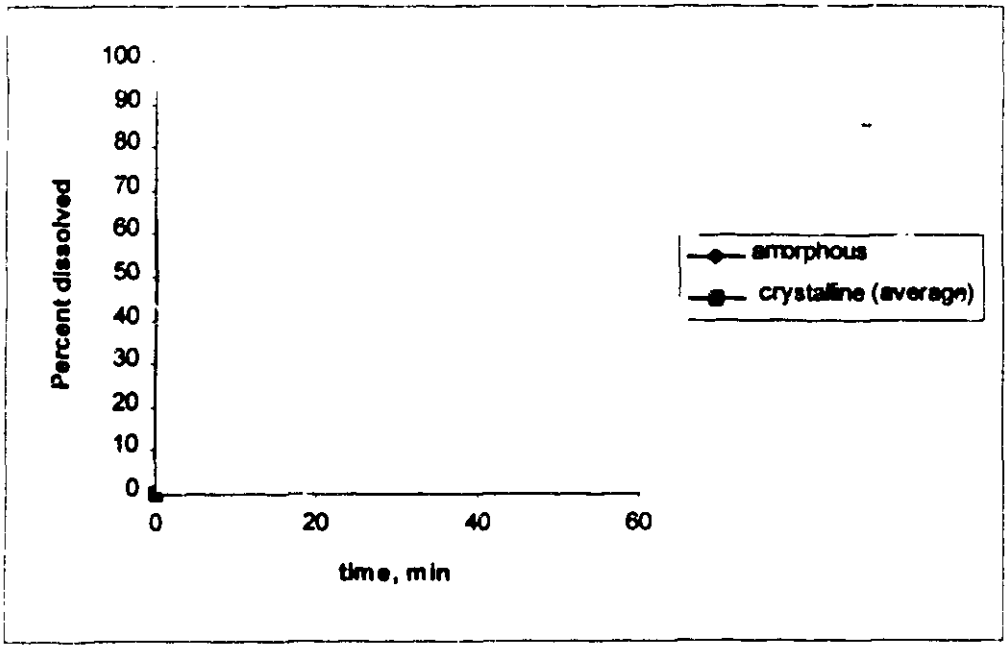


Figure 3: Comparison of atorvastatin dissolution profiles in water in amorphous vs. crystalline tablet formulations—40 mg

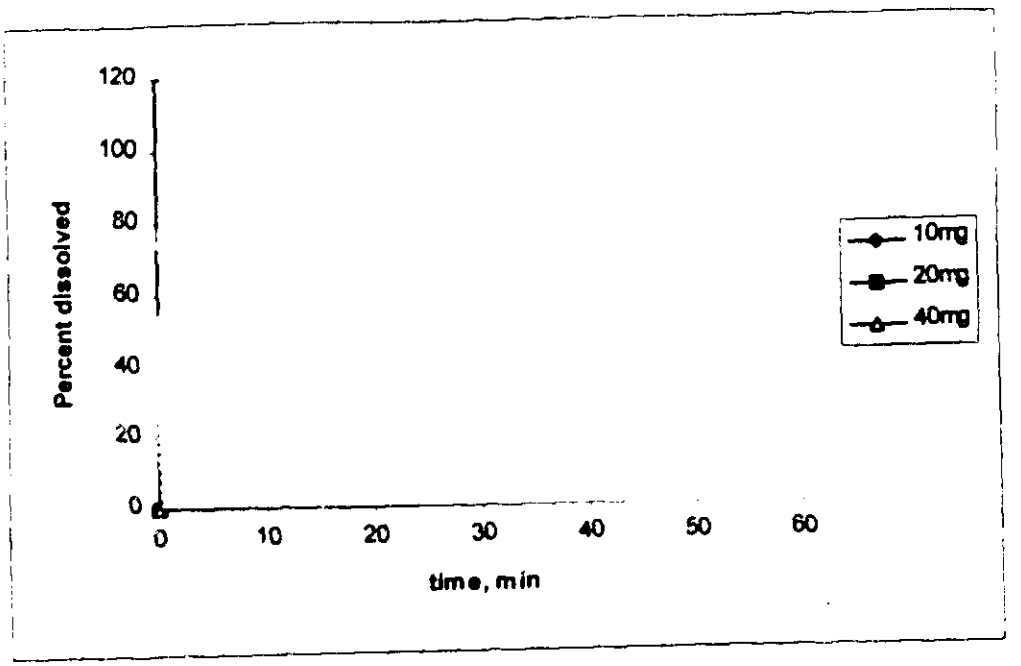


Figure 4: Comparison of atorvastatin dissolution profiles in water in 10, 20 and 40 mg dosage forms

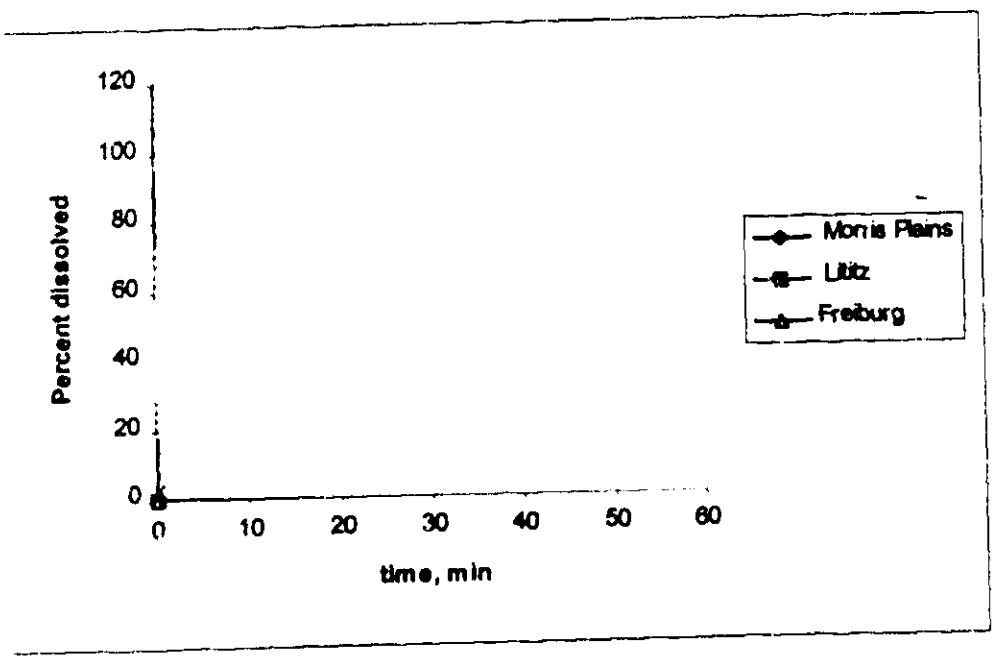


Figure 5: Comparison of atorvastatin dissolution profiles in water (40 mg) at three different manufacturing sites

ANALYTICAL METHODOLOGY:

The majority of the clinical pharmacology studies were conducted using an

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Bioavailability/Bioequivalence

A. Absolute Bioavailability

B. Bioequivalence

Five bioequivalence studies were included as part of this NDA. Two of these studies evaluated the 10 mg dosage. The market-image crystalline formulation was compared to a clinical trial amorphous formulation

was used in an attempt to decrease intrasubject variability. In this study mean t_{max} and C_{max} values of the crystalline form were nearly 2-fold shorter and 50% higher, than those observed in the amorphous form. Percent RSD values approached or were greater than 50% for C_{max} and $AUC_{(0\text{-}tldc)}$ in both treatment arms. T_{max} %RSD values were greater than 110%. The use of atorvastatin as an internal standard lowered C_{max} %RSD values from 71% to 35% and 56% to 29% for the market-image crystalline and amorphous tablets, respectively. $AUC_{(0\text{-}tldc)}$ %RSD values were reduced from ~50% to 5%-10%. Furthermore, the confidence intervals decreased by half. A statistically significant period effect was observed and most apparent in C_{max} values, but was insignificant and overshadowed by the extreme variability of the parameter values (Treatment pvalue=0.002, period pvalue=0.02). No detectable concentrations prior to dosing period 2 were observed as confirmatory evidence of this period effect (See Table 4).

TABLE 4. Plasma Atorvastatin Pharmacokinetic Parameter Values Following Administration of 10 mg Atorvastatin Tablets (N=36)

Parameter	Treatment Least Squares Means		Ratio[a]	90% CI[b]
	Market Image *Crystalline*	Clinical Lot *Amorphous*		
C_{max}[c], ng/ml	4.57	3.18	144	124-166%
$AUC_{(0\text{-}tldc)}$[c], ng·hr/ml	36.7	34.3	107	101-114%
C_{max}Ratio[c,d]	0.83	0.62	134	122-146%
AUCRatio[c,d]	0.95	0.88	108	105-111%

[a]Ratio of market-image to clinical-lot tablets expressed as a percentage of clinical-lot tablet
[b]Confidence intervals based on log-transformed values
[c]Values are antilogs of least-squares mean log-transformed values
[d]C_{max}Ratio and AUCRatio values are ratios of atorvastatin/[$^2H_5$] atorvastatin parameter values

In an earlier study without the C_{max} was 23% higher and $AUC_{(0\text{-}tldc)}$ 11% higher in the crystalline form compared to the amorphous based on the analysis of the natural log-

transformed parameters. The two tablets were not bioequivalent, although the extent of absorption was similar, the rate was significantly higher in the crystalline tablet at the 90% confidence interval. The %RSD for both AUC and C_{max} was ~44%. No period effect was present.

Atorvastatin and atorvastatin equivalent pharmacokinetic parameter values were highly variable in both studies. Although the use of an internal standard lowered variability, the conclusions drawn from both studies were the same; AUC was equivalent, but C_{max} was not at the 90% confidence interval.

A bioequivalence study was also conducted to evaluate the 40 mg tablet in three different formulations: amorphous clinical trial, nonmarket-image crystalline (MOPS-manufactured at Morris Plains facility) and market-image crystalline (Lititz facility). Neither of the crystalline formulations were bioequivalent to the amorphous form; although extent of absorption was similar, C_{max} at the 90% confidence interval was not. C_{max} values were 50% higher in the two crystalline forms compared to the amorphous. The two crystalline formulations were bioequivalent. C_{max} and $AUC_{(0\text{-}tldc)}$ % RSD values were greater than 48%.

TABLE 5. Plasma Atorvastatin Pharmacokinetic Parameter Values Following Administration of 40 mg Atorvastatin Tablets

Parameter	Treatment Least Squares Means			Ratio[b]	90% CI[c]
	Market Image *Crystalline* Lititz	Clinical Lot *Amorphous*	Nonmarket Image *Crystalline* MOPS		
C_{max}[a], ng/ml	27.15	18.37	27.84	148 L/C 98 L/M 152M/C	128-171% 85-113% 131-176%
$AUC_{(0\text{-}tldc)}$[a], ng·hr/ml	148.4	133.2	145.5	111 98 109	104-119% 96-109% 102-117%
C_{max}Ratio[d]				135 103 140	124-151% 88-108% 127-155%
AUCRatio[d]				108 101 109	105-111% 96-102% 106-112%

[a]Values are antilogs of least-squares mean log-transformed values
[b]expressed as a percentage of
[c]Confidence intervals based on log-transformed values
[d]C_{max}Ratio and AUCRatio values are ratios of atorvastatin/[$^2H_5$] atorvastatin parameter values

The final two bioequivalence studies compared both the 10 mg and 40 mg market-image tablets manufactured at two different sites (Freiburg and Lititz). The 10 mg tablets were bioequivalent. However, the 40 mg tablets using the standard method of determining bioequivalence were not bioequivalent. When the sponsor employed the method, the computed 90% confidence intervals did fall within the 80-125% range.

The study design for the bioequivalence studies was not adequate and the results were inaccurate. In all of these studies the first time point was taken at 0.5 h. This time point was too late to properly characterize C_{max}. Fifty percent of the subjects in some of these studies had already reached C_{max} at 0.5 h.

TABLE 6. Plasma Atorvastatin Pharmacokinetic Parameter Values Following Administration of 10 and 40 mg Atorvastatin Tablets (N=36)

Parameter	Treatment Least Squares Means		Ratio[a]	90% CI[b]
10 mg	Lititz	Freiburg		
C_{max}[c], ng/ml	3.84	3.69	96	83-111%
$AUC_{(0\text{-}tldc)}$[c], ng·hr/ml	30.9	27.7	90	82-98%
C_{max}Ratio[c]	0.84	0.80	95	85-109%
AUCRatio[c]	0.97	0.96	99	97-103%
40mg				
C_{max}[c], ng/ml	28.1	23.8	85	73-98%
$AUC_{(0\text{-}tldc)}$[c], ng·hr/ml	141.8	141.7	100	94-106%
C_{max}Ratio[c]	0.96	0.88	92	83-103%
AUCRatio[c]	0.99	0.97	98	97-100%

[a]Ratio of market-image to clinical-lot tablets expressed as a percentage of clinical-lot tablet
[b]Confidence intervals based on log-transformed values
[c]Values are antilogs of least-squares mean log-transformed values

C. *Food Effects*

A food effect study was performed using the bulk form of the drug in a gelatin capsule. Sixteen healthy volunteers (10 males and 6 females) participated in the nonblind, randomized 2-way crossover study. They were given 80 mg of atorvastatin in the morning with either 8 oz of water

or with a medium fat meal (cereal, 2 eggs without fat, 2 slices white toast with 2 teaspoons of margarine and 8 oz 2% milk). Blood samples were collected over a period of 72 hours and analyzed using A one week washout period was observed. On Day 8, 15 out of 16 subjects exhibited predose concentrations of atorvastatin equivalents. Pharmacokinetic parameters were not adjusted. Although the rate of atorvastatin absorption significantly decreased in the presence of food, the extent of absorption did not change. Mean C_{max} values, $AUC_{(0-\infty)}$ and $AUC_{(0\text{-}tldc)}$ decreased in the presence of food, 47.8 %, 15.4% and 12.7% respectively. A small statistically significant sequence effect was evident for the Cmax value only. Mean t_{max} increased by 124%, from 2.6 to 5.9 hours. This study was not repeated using the crystalline form of the drug.

Two additional food effect studies were conducted to determine the lipid-lowering effects and pharmacokinetic characteristics of atorvastatin administered once daily either with an evening meal or 3 hours after the meal. Sixteen healthy volunteers (7 males and 9 females) were evaluated. One study used the crystalline form, the other the amorphous form of atorvastatin. Patients were administered identical breakfasts, lunches and dinners. The dinner consisted of 3 ounces baked turkey breast without skin, 1 cup mashed potato, ½ cup peas, 1 cup tossed salad, 2 tablespoons low calorie dressing, two 1-ounce dinner rolls with 2 teaspoons corn oil margarine, ½ cup vanilla ice milk, 1 medium orange, and 8 ounces water. With the crystalline tablet, a 25% decrease in C_{max}, a 29.8% increase in t_{max} and a 8.6% decrease in $AUC_{(0-24)}$ was observed with a meal. However, these significant pharmacokinetic differences were not reflected in the pharmacodynamic performance of the drug. After two weeks of treatment, similar reduction for both treatment phases was observed for TC and LDL-C. However, a 4-fold decrease in triglycerides was observed in the presence of a meal. Although statistically significant, the difference was not clinically significant due to the day-to-day variability in triglycerides (Figure 2).

For the amorphous tablet, changes in C_{max} were similar to the crystalline tablet. However, the increase in t_{max} was 2x values observed in the crystalline tablet and $AUC_{(0-24)}$ was 21.5% lower in the presence of food.

TABLE 7. Least squares mean atorvastatin-equivalent pharmacokinetic parameter values following administration of 10 mg atorvastatin QD (crystalline) for 15 days in the evening with meals and after meals (N=15)

Parameter	With Meals	After Meals	Difference (%)	95% Confidence Interval
Cmax[a], ng eq/mL	5.31	7.10	-25.2	-34.5 to -14.5
tmax, hr	4.4	3.4	29.8	-50.6 to 110.1
AUC(0-24)[a], ng eq·hr/mL	83.9	91.8	-8.6	-23.1 to 8.6

[a] Based on analysis of natural log transformed parameter estimates

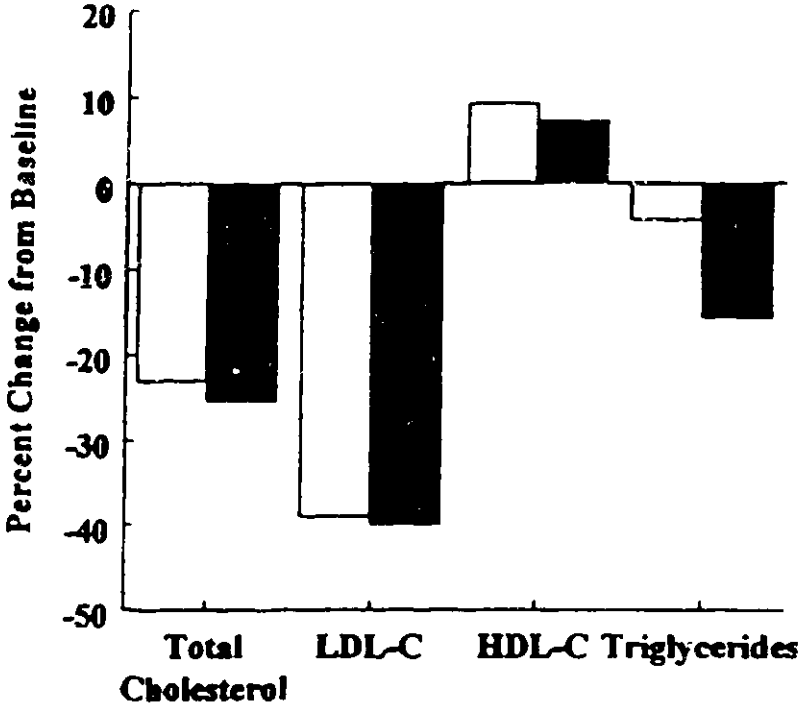


Figure 2: Least squares mean change from baseline in lipid measurements following 2 weeks of atorvastatin (crystalline) with meals (■) or after meals (□) (N=15)

D. Diurnal Effects

An open label, randomized two-way crossover, multiple-dose study to evaluate morning vs. evening administration of atorvastatin in 16 healthy subjects (9 men and 7 women) was conducted. Subjects received 40 mg atorvastatin each morning or evening for 2 weeks with a 4 week washout period. Blood samples were collected for 48 hours for pharmacokinetic analysis. One subject was withdrawn from the study due to elevated LDH, AST and ALT values.
The rate and extent of atorvastatin absorption was reduced in the evening. Mean C_{max} was 30.6% lower, mean t_{max} 56.8% later and $AUC_{(0-24)}$ was 28.9% lower. Mean elimination half-life at 16 hours in the morning was similar to 12.9 hours in the evening. The lipid lowering effects were comparable with total cholesterol and LDL-C levels reduced 34% and 48% respectively. Twice as many adverse events were reported in the morning treatment group compared to the evening with headache being the most frequently reported adverse event.

II. Pharmacokinetics

A. Intrasubject/Intersubject Variability

The administration of atorvastatin is associated with large variability as evidenced by percent relative standard deviation (%RSD) values for pharmacokinetic parameters ranging from 30-50%. Intrasubject and intersubject variabilities were assessed in a nonblind 3-period repeated measures type study. Eighteen healthy subjects (13 males and 5 females) received 40 mg of atorvastatin (amorphous form) under fasting conditions in the morning on three separate occasions, one week apart. Serial blood samples were collected over 72 hours. C_{max} values ranged from 29.9 to 33.7 with a grand mean of %RSD of 30.4%. AUC(0-∞) ranged from 31.8 to 35.2 with a grand mean of %RSD of 30.8. Tmax, values ranged from 1.5 to 2.1 with a grand mean of %RSD of 72.2. Intrasubject variability accounted for 66.1% of the variability in Cmax and intrasubject variability is also suspected to be the major contributor to tmax variability as well. Intersubject variability accounted for 75.4% of the variability in $AUC_{(0-\infty)}$. Elimination half-life variability was equally distributed between inter- and intrasubject variability. The first collection time point for this study was at t=1 h. Earlier time points should have been taken because 50% of the subjects reached C_{max} at this first time point. However this problem in study design did not negate the ability to quantitate intrasubject and intersubject variabilities.

A study was also conducted to evaluate intrasubject and intersubject variabilities comparing a 10 mg amorphous atorvastatin tablet to a 1 mg/ml [d_5] atorvastatin solution in twelve healthy subjects (8 males and 4 females). Subjects received single doses on two separate occasions. The variability observed in pharmacokinetic parameters was again high and found to be intrinsic to the drug rather than the formulation characteristics. Again C_{max} variability was attributed to intrasubject variability (69%) and $AUC_{(0-tldc)}$ was primarily intersubject variability (69-80%). However, the use of the method and the determination of a C_{max} ratio and an AUC ratio reduced C_{max} intrasubject variability from 41% to 31% and $AUC_{(0-tldc)}$ intrasubject variability from 24.8% to 10%. The sponsor believes by using this method the chances of declaring two drugs bioequivalent can be vastly improved. However, so much of this improvement is dependent on %RSD values obtained in a given study. The two studies were in agreement in their determinations of intrasubject and intersubject variabilities.

B. Normal Volunteers

Atorvastatin absorption was rapid following oral administration with C_{max} occurring in 2 hours. Mean terminal elimination half-life was 11.6 hours in humans, 15.6 hours in dogs and 18.9 hours in rats. Distribution was extensive with a mean Vd_β of 565 L. Following IV infusion, atorvastatin declined in a biphasic manner. Hepatic plasma flow was approximately 800 ml/min and mean clearance of 603 ml/min yielded a predicted mean extraction ratio of 75.5%. Maximal predicted systemic availability was 24.5% but the actual mean value for the oral dose was 12.2% which indicated incomplete absorption and possible extrahepatic metabolism. Multiple secondary peaks were observed by compared to one secondary peak observed by which suggested possible enterohepatic recycling . Active metabolites accounted for 22% of the profile after IV administration, and 69% of this profile following oral administration which suggested many of these active metabolites were possibly formed during absorption.

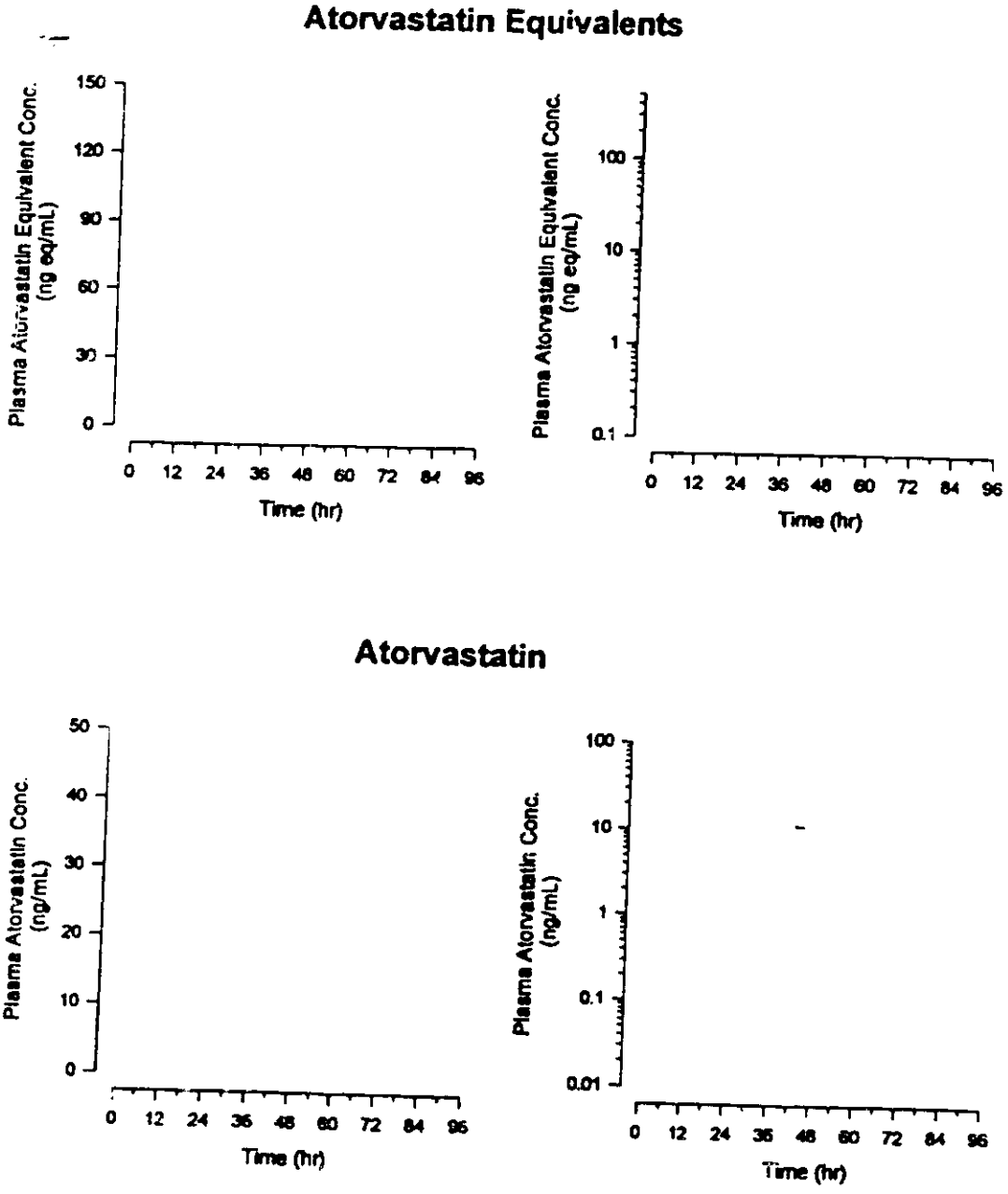
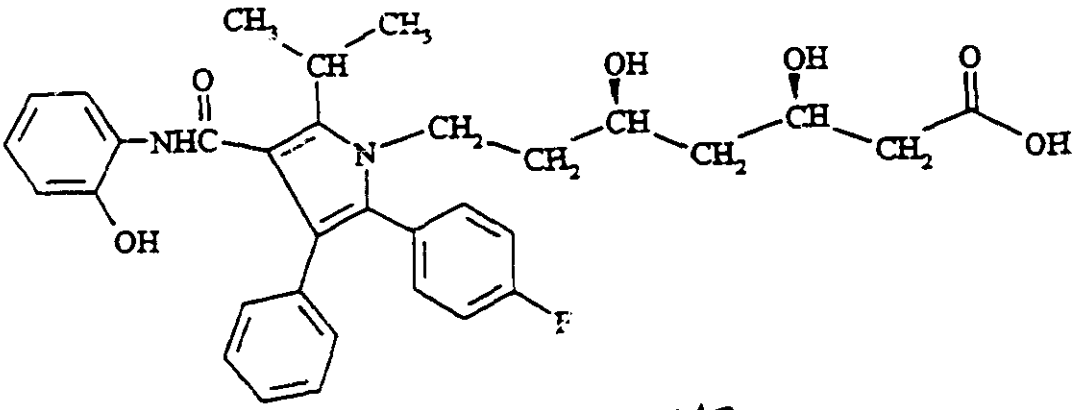


Figure 6: Mean plasma atorvastatin-equivalent and atorvastatin concentration-time profiles following administration of 10(●), 20(○), 40(▲) and 80(△)mg atorvastatin QD (N=16)

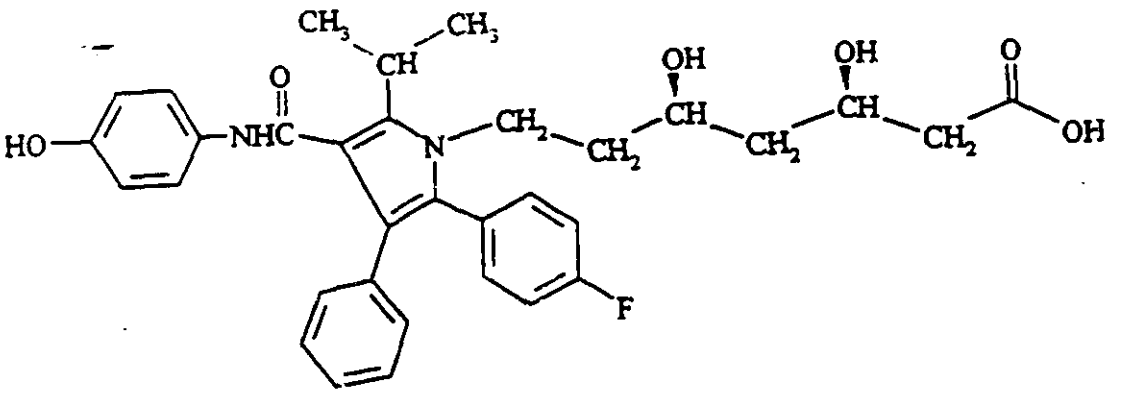
III. Metabolism

A mass balance study in plasma, urine and feces was conducted in 6 healthy male volunteers who were administered 20 mg atorvastatin (capsule form) daily for 2 weeks. The majority of the dose was excreted in the feces 98.4% with 1.23% found in the urine. Multiple metabolites were found in plasma, urine and feces. Plasma radioactivity $t_{1/2}$ for [^{14}C]atorvastatin was 62.5 hours, $t_{1/2}$=30 hours for atorvastatin equivalents and $t_{1/2}$=12.6 hours for atorvastatin. These half-live differences suggest the presence of other long-lived metabolites in plasma that do not inhibit

When atorvastatin was evaluated in the rat, dog and human microsomal preparations there was no difference in the metabolic profiles. In all three species, metabolites M1 and M2 were the only major metabolic products formed. The M1 peak area ratio obtained for the dog, rat and human microsomes was 1.5:1.4:0.5 respectively suggesting similarity in the formation of this metabolite. M1 represents the parahydroxy metabolite and M2 the orthohydroxy metabolite.



PD 152873 – M2



PD 142542 – M 1

Figure 7: Ortho- (M2) and (M1) parahydroxy metabolites of atorvastatin

Human hepatocytes were also studied as a method of prediction of in vivo metabolism. Due to the degradation of atorvastatin at -80° C the study was not very conclusive. However three metabolites were identified; the two hydroxylated compounds and a beta-oxidized product. The metabolites were not further metabolized by cytochrome P450 enzymes.

In vitro hepatic and intestinal microsomal metabolism studies which express CYP 1A1, 1A2, 2A6, 2B6, 2D6, 2E1 and 3A4 were evaluated. Only 3A4 metabolized atorvastatin to the two active monohydroxy metabolites. The inhibition was marginal with <10% at 5μm. The apparent K_m and V_{max} values for the formation of the metabolites were 71.8 ± 6.7 μM and 1.07 ± 0.04 nmoles/min/mg microsomal protein for M2 and 79.9 ± 7.8 μM and 0.14 ±0.01 nmoles/min/mg microsomal protein for M1. A 10-fold difference in formation was observed between the two metabolites with M2 forming much faster.

When atorvastatin was incubated with inhibitors such as: furafylline (1A2), gestodene and ethinyl estradiol (3A4), sulphaphenazole (2C9), quinidine (2D6) and diethyldithiocarbamate (2E1), the two 3A4 compounds blocked formation of the two active metabolites approximately 90% and 60%, respectively. No relative differences in the magnitude of formation of the metabolites were observed as a result of the exposure of atorvastatin to the 3A4 inhibitor compounds. IC_{50} values were similar between atorvastatin and its metabolites (atorvastatin =3.71, M1=3.29 and M2=5.54). The beta-carbon oxidized atorvastatin acid had no activity. Intestinal microsomes metabolized atorvastatin to the two active metabolites indicating a role for the intestines in the biotransformation of atorvastatin.

Atorvastatin is a chiral 5R,3R HMG-CoA reductase inhibitor with 5R,3S and 5S,3R-diastereoisomers and 5S,3S-enantiomers. It does not isomerize into the various diastereoisomers.

The sponsor did not perform a thorough characterization of the metabolites because the disposition of the metabolites was not determined. Most of the studies conducted expressed or quantitated the data as atorvastatin equivalents (parent drug and metabolites).

Plasma protein binding was approximately 98% with no difference between species (dog, rat, mouse and humans). The major binding proteins for atorvastatin were: serum albumin (95%), LDL (98%) and HDL (97%).

IV. Dose and Dosage Form Proportionality

An open-label multiple-dose, dose escalation study using the crystalline form was conducted in 15 healthy volunteers (8 males and 7 females) using 10, 20, 40 and 80 mg doses of atorvastatin administered every morning for 8 days. Samples were collected before and up to 96 hours. This study demonstrated that mean atorvastatin-equivalent C_{max} increased more than proportionally with increasing dose, especially at the 80 mg level. This nonlinearity could be attributed to the performance of the active metabolites. The $AUC_{(0-24)}$ was linear over the tested range. Similar

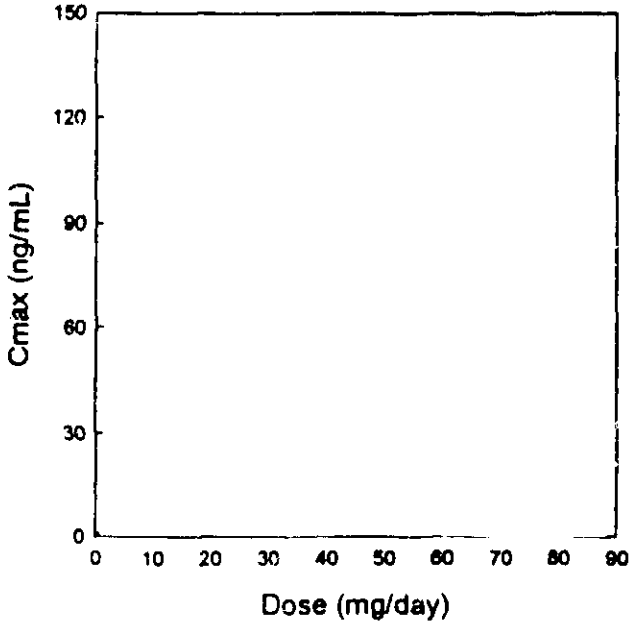
mean t_{max} values for atorvastatin-equivalents were observed for the four dosage groups. The elimination half-lives for the atorvastatin equivalent, atorvastatin and active metabolites were 23, 13 and 30 hours, respectively. No dose dependence in half-life was observed. Deviations in dose-linearity were also observed for C_{min} which decreased less than dose proportionally. During the 24-hour dosing interval 30% of circulating atorvastatin equivalent activity was due to unchanged atorvastatin.

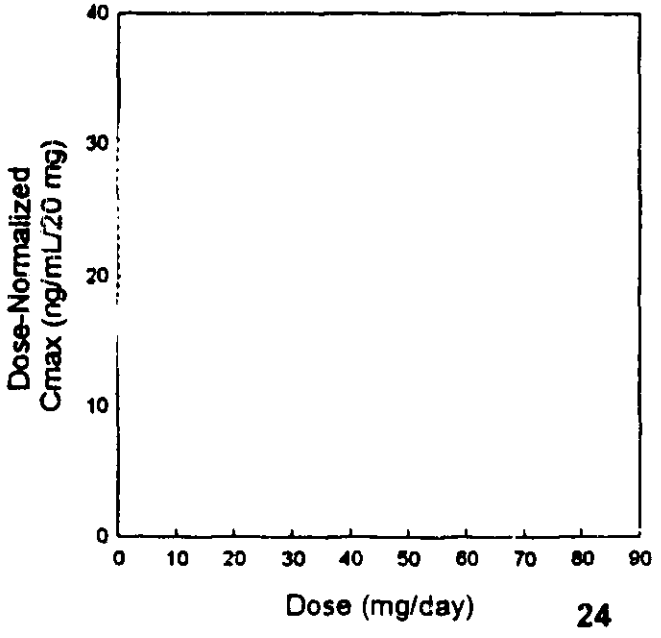
It was observed that C_{min} decreased with dose and C_{max} increased with dose. Normally these two parameters would move in the same direction. The sponsor's explanation was that atorvastatin and its active metabolites underwent intensive saturable binding to a high affinity peripheral receptor in the tissue. This explanation is reasonable when one considers the large volume of distribution of atorvastatin (565 L) (see Table 10).

Atorvastatin equivalent concentration, measured using the assay was ~2.5 x higher than atorvastatin concentration which was measured by This was observed up to the 80 mg dose.

Dose linearity was also evaluated with the amorphous tablet with similar results. Twenty-four subjects (19 males and 5 females) with elevated cholesterol levels were given 5, 20 and 80 mg tablets daily in the morning over a period of six weeks. Percent reduction in LDL-C (Friedewald) and LDL-C (Beta Quant) were highly correlated, r=0.95. Reductions were also observed using the LDL-Apo B assay and these reductions were correlated with both LDL-C measures (Friedewald and Beta-Quant), r=0.90. These changes were observed within 24 hours of initiation of dose with 5 mg. Adverse events were classified as mild to moderate and included headaches, eye irritation and constipation. Two subjects had either abnormal ALT and GGT levels or GGT and alkaline phosphatase levels which were possibly related to atorvastatin administration.

Atorvastatin





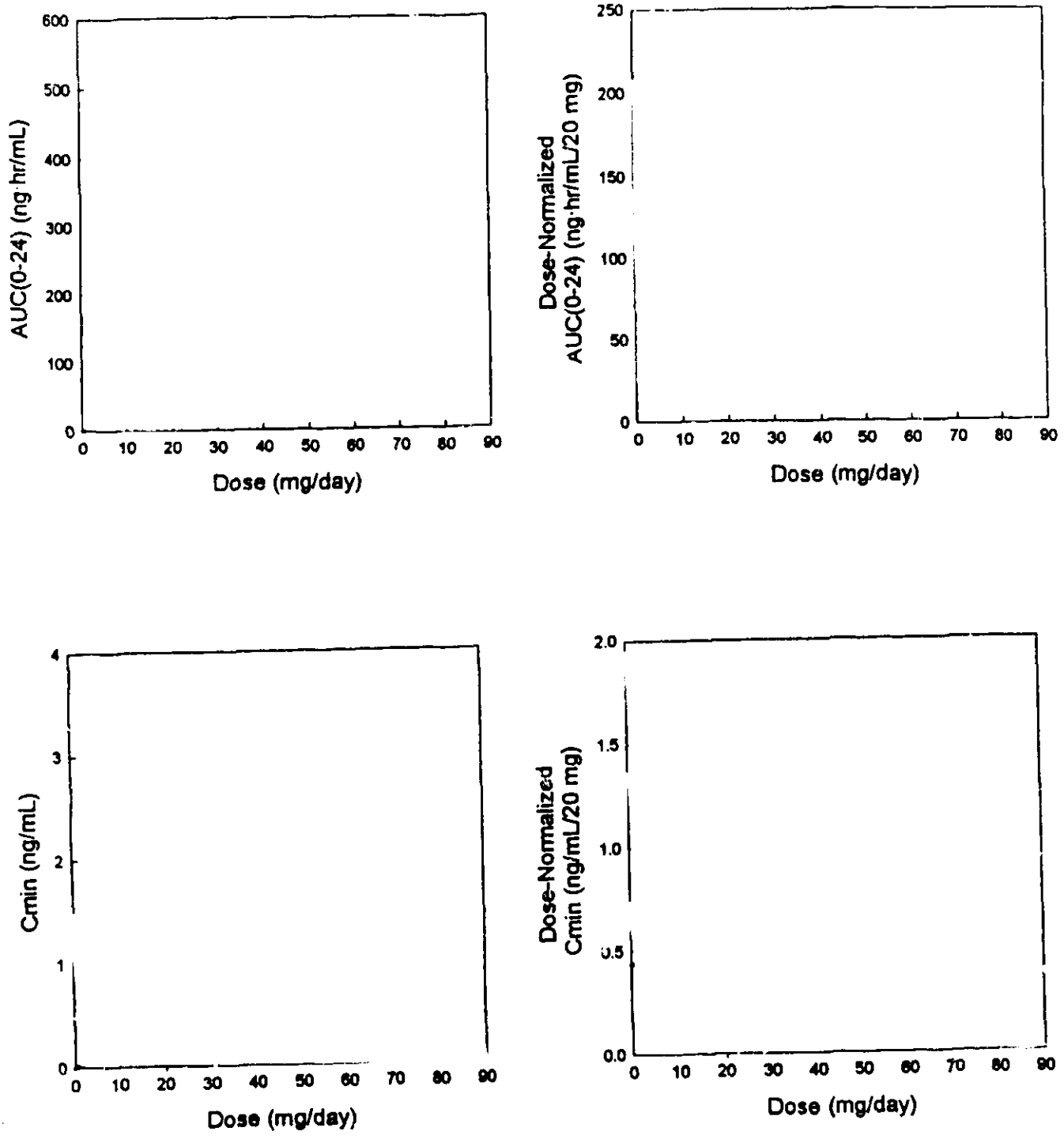


Figure 8: Individual Cmax, AUC(0-24) and Cmin values for atorvastatin following administration of atorvastatin QD

TABLE 10. Summary of least-squares mean of atorvastatin, atorvastatin-equivalents and active metabolites pharmacokinetic parameters following administration of 10, 20, 40 and 80 mg atorvastatin QD

Parameter	10 mg/day	20 mg/day	40 mg/day	80 mg/day
Atorvastatin Equivalents (EIA)				
Cmax (ng eq/mL)[a]	9.85	22.6	48.3	139
nCmax (ng eq/mL/20 mg)[a]	19.7	22.6	24.2	34.9
AUC(0-24) (ng eq·hr/mL)[a]	116	248	370	990
nAUC(0-24) (ng eq·hr/mL/20 mg)[a]	233	248	185	248
Cmin (ng eq/mL)[a]	2.04	3.43	3.19	4.33
nCmin (ng eq/mL/20 mg)[a]	4.09	3.43	1.60	1.08
tmax (hr)	3.47	1.70	1.43	1.80
t½ (hr)	30.1	23.1	18.3	20.0
Atorvastatin (GC/MS)				
Cmax (ng/mL)[a]	4.06	10.0	25.2	54.6
nCmax (ng/mL/20 mg)[a]	8.12	10.0	12.6	13.7
AUC(0-24) (ng·hr/mL)[a]	37.2	72.1	142	270
nAUC(0-24) (ng·hr/mL/20 mg)[a]	74.3	72.1	71.1	67.4
Cmin (ng/mL)[a]	0.428	0.589	0.738	0.797
nCmin (ng/mL/20 mg)[a]	0.857	0.589	0.369	0.199
tmax (hr)	0.60	1.00	1.00	1.10
t½ (hr)	12.2	13.0	10.7	15.1
Active Metabolites (Difference Between EIA and GC/MS)				
Cmax (ng eq/mL)[a]	6.53	14.9	26.6	93.9
nCmax (ng eq/mL/20 mg)[a]	13.1	14.9	13.3	23.5
AUC(0-24) (ng eq·hr/mL)[a]	78.9	170	220	716
nAUC(0-24) (ng eq·hr/mL/20 mg)[a]	158	170	110	179
Cmin (ng eq/mL)[a]	1.59	2.71	2.28	3.44
nCmin (ng eq/mL/20 mg)[a]	3.18	2.71	1.14	0.859
tmax (hr)	3.87	3.83	2.70	2.13
t½ (hr)	32.8	30.9	32.1	23.6

[a] Value represents back transformation of least-squares mean of log-transformed value

V. Special Populations

Renal

Twenty subjects (14 men and 6 women) ranging in age from 19 to 69 years were given 10 mg atorvastatin once daily for 14 days. Subjects were divided into three groups according to their estimated creatinine clearance values. The three groups were: < 30 ml/min (N=8, of which three were < 15 ml/min), >30 and < 60 ml/min (N=6), and >60 ml/min (N=6). Regression of pharmacokinetic parameter values on Clcr indicated a statistically significant correlation for the elimination rate constant only. No significant increases were observed for $AUC_{(0-24)}$ and C_{max} values. Pharmacodynamic values, % total cholesterol, LDL-C, HDL-C and TG were not significantly different in patients with renal impairment. Therefore, renal impairment has no significant impact on the pharmacokinetics and pharmacodynamics of atorvastatin and its metabolites. Therefore no adjustments in administration are required for this population.

Hepatic

Eighteen males (two of which were later withdrawn---one due to adverse event, the other due to lack of compliance) ranging in age from 31 to 63 years of age were graded for hepatic insufficiency using the Childs-Pugh analysis and were categorized as either healthy, Childs-Pugh A or Childs-Pugh B with Childs-Pugh B being the most severe (healthy N=8, Childs-Pugh A N=5, Childs-Pugh B N=3). These hepatically impaired patients were age and sex matched with normal healthy volunteers. Subjects were given 10 mg doses of atorvastatin daily for 14 days. No significant changes were observed in ECGs or vital signs. Hepatically impaired patients showed a 7-fold and 5-fold increase in C_{max} and $AUC_{(0-24)}$, respectively. When separated by degree of hepatic insufficiency both AUC and C_{max} were 4x greater for the Childs-Pugh A group and 12x greater for the Childs-Pugh B group. There were no significant differences in elimination half-life or mean t_{max}. Lipid responses for healthy subjects and impaired subjects were similar. When one normal subject who appeared as an outlier was excluded from the analysis, the differences approached significance. The mean baselines were lower for total cholesterol, LDL-C and triglycerides in hepatically impaired groups. The percent decrease in total cholesterol, LDL-C and triglycerides was smaller for Childs-Pugh B patients compared to the other two groups but did not approach statistical significance; probably because of the small sample size. Although, atorvastatin is useful in its lipid-lowering effects in hepatically impaired patients it should not be prescribed in these patients because of the significant changes in pharmacokinetic parameters.

Age and Gender

Age and sex effects were studied in 32 healthy volunteers divided into two groups (18-35 years and 65 years and older) who were administered a single 20 mg oral dose of atorvastatin. Each group included 8 males and 8 females. AUC values were 27% greater, mean elimination half-life values 36% longer, and mean C_{max} and t_{max} values were 43% higher and 5% earlier, respectively,

in elderly subjects compared to young subjects. Mean AUC(0-∞) and C_{max} were approximately 34% and 32% higher, respectively, in elderly females than in young females, and 22% and 55% higher, respectively, in elderly males compared to young males. The elimination half-life was 95% longer in elderly females compared to the young. In men, however this difference was not readily apparent. One of the young males had an excessively long $t_{1/2}$ of 50.7 hours. When this value was eliminated, the $t_{1/2}$ of the elderly males was 54% longer than that of the young. Females compared to males achieved mean $AUC_{(0-\infty)}$ 11% lower, $t_{1/2}$ 20% shorter, mean C_{max} 18% higher and t_{max} values 40% shorter. All adverse events reported were minor. Most cases were headaches with a higher incidence in the young compared to the elderly. The age differences observed are probably related to the physiological changes common to aging. These age and gender differences should be further assessed in the subsequent clinical trials and the population PK study included as part of this NDA.

Pediatric

No studies were conducted in pediatric populations.

VI. Drug Interactions

Twelve healthy male adults were used to investigate the effect of atorvastatin on antipyrine clearance. Subjects received 600 mg antipyrine on Days 1 and 22 and 80 mg atorvastatin on Days 8-23. Individual and mean antipyrine kinetics were similar in both treatments. There were no clinically-related changes in blood pressure, heart rate or ECG assessments. Atorvastatin had no effect on antipyrine clearance.

In the evaluation of an atorvastatin/cimetidine interaction, twelve healthy subjects received 10 mg atorvastatin daily for 15 days or 300 mg cimetidine for 17 days with the aforementioned dosage of atorvastatin. The only pharmacodynamic difference observed was the decrease in triglycerides between atorvastatin alone, 33.8%, and with cimetidine coadministration 25.8% (a mean difference of 8%). The clinical implications are probably irrelevant and within the parameters of the day-to-day within subject variability of triglycerides. The pharmacokinetic evaluation of atorvastatin was confounded. The t_{max} value was 0.9 h shorter when the two drugs were coadministered. However, most of this difference was attributed to one patient who had a 10h t_{max}. The C_{max} value was 11.2% lower when atorvastatin was coadministered, and the AUCs were similar. The coadministration of cimetidine significantly lengthened the half-life of atorvastatin (17.0 vs. 10.1 h). The sponsors initial explanation for this difference was: 1) enterohepatic cycling and 2) several plasma concentration time points close to the detection limit. However, later studies proved that the drug does not undergo enterohepatic cycling. No changes in C_{min} for atorvastatin were observed during the study. Cimetidine is a known inhibitor and either the metabolism of atorvastatin was altered or gastric pH. With the current study design where atorvastatin equivalents were evaluated rather than parent drug and metabolites the exact mechanism cannot be elucidated. These two drugs can be coadministered, however, safety especially at the higher dosages is a concern due to possible accumulation.

Eighty milligrams of atorvastatin were administered either with 0.25 mg digoxin or without, on a daily basis. Atorvastatin, like the other HMG-CoA reductase inhibitors caused a significant increase (C_{max} 20%, C_{min} 22% and $AUC_{(0-24)}$ 15%) in the extent of digoxin absorption. Plasma concentration of atorvastatin was monitored during the study period with no significant changes. No pharmacokinetic study was conducted for atorvastatin. When administered concomitantly, consideration should be given in the adjustment of digoxin considering its narrow therapeutic range and concerns with toxicity. Secondly, this study was performed using the amorphous form of the drug. Use of the crystalline form will cause an even greater difference. The effect of atorvastatin pharmacokinetics by digoxin was not studied.

Eight males and four females were administered 10 mg atorvastatin daily for 15 days. In the comparative arm of the study, 10 mg atorvastatin was given daily for 15 days and 30 ml Maalox® TC suspension was given four times a day for 17 days (two-way crossover design). Both the rate and extent of absorption of atorvastatin was decreased in the presence of Maalox® TC. T_{max} was 96% longer, C_{max} 34% lower and $AUC_{(0-24)}$ 34% lower. The half-life also decreased with the coadministration of Maalox® TC, however the terminal elimination-rate constant was not evaluated for several subjects due to the presence of secondary peaks and atorvastatin concentrations at the lower limit of quantitation. Significant period and sequence effects were observed for atorvastatin equivalents for C_{max} and $AUC_{(0-24)}$ ($p=0.01$ and $p= 0.003$---period and $p=0.0001$---sequence). However, these parameters did not influence the effect of Maalox® TC on atorvastatin pharmacodynamic performance. LDL-C and cholesterol reduction were similar between the two treatments. However, the mean decrease in triglycerides was less in the presence of the Maalox® TC and this decrease was statistically significant. Increased incidence of adverse events mostly GI related (diarrhea, flatulence) were apparent with the coadministration of the Maalox® TC and probably attributed to the presence of this compound. Atorvastatin can be coadministered with Maalox® TC with no effect on its lipid-lowering abilities.

Warfarin has a narrow therapeutic index and its pharmacodynamics are known to be affected by coadministration of other drugs which are extensively metabolized. Therefore, atorvastatin coadministered with warfarin was also evaluated. Nine male and three female patients receiving stable, chronic warfarin therapy were given 80 mg atorvastatin every day in the morning on an empty stomach for 15 days and blood samples were collected daily prior to drug administration for prothrombin determination (PT). A final PT was taken 14 days after the last dose. A decrease in PT of 1.67 ± 0.425 seconds was observed during the first four days of treatment. However, by the conclusion of the study PT had returned to normal. This decrease was not clinically significant and adjustment of dosage is not necessary, however, clinicians should monitor their patients closely upon initiation of therapy.

Both atorvastatin and ethinyl estradiol are metabolized by CYP 3A4, a potential for a drug interaction exists. Sixteen healthy females were exposed to the concurrent administration of three 21-day cycles of Ortho-Novum 1/35 oral contraceptive and during the third cycle 40 mg of

atorvastatin. Ortho-Novum contains 1 mg norethindrone and 0.035 mg ethinyl estradiol. Coadministration of atorvastatin with Ortho-Novum 1/35 increased systemic exposure to ethinyl estradiol and norethindrone. The C_{max} value for ethinyl estradiol was 30% higher and the extent of absorption was 20% higher. Mean $t_{1/2}$ values were similar, however minor differences were observed in t_{max}. Concomitant administration with norethindrone increased C_{max} and $AUC_{(0-24)}$ values 24% and 28% respectively, with negligible effects on t_{max}. No increase in the frequency of adverse events or changes in vital signs were observed with the concomitant administration of the drugs. These two drugs can be used together, however any situation where elevated levels of estrogen are of concern, physician monitoring is important.

Twelve male and female subjects were exposed to the macrolide antibiotic erythromycin a known substrate of the CYP 3A4 enzyme. Reports of rhabdomyolysis occurrence with the concomitant administration of other cholesterol lowering agents such as lovastatin has been documented. A 10mg atorvastatin tablet was given either alone or in conjunction with one 500 mg Ery-Tab® given QID from 7 days before through 4 days after the atorvastatin dose with a two week washout interval in-between. An increase in adverse events was reported when the two drugs were coadministered. None were serious, but the majority were gastrointestinal complaints. C_{max} and $AUC_{(0-\infty)}$ values of atorvastatin, following administration of both drugs, were 37.9% and 32.5% respectively, higher than when administered alone. The mean t_{max} values were substantially reduced ~60%. The terminal elimination half-life could not be properly characterized.

Bile-acid binding resins such as colestipol and other HMG-CoA compounds have been used in combination therapy to reduce lipid levels. This combination therapy has been shown to achieve lower levels than those obtained when the two agents are administered alone. However, this regimen has many undesirable side effects, most commonly GI, and they are associated with the colestipol administration.

Two studies were conducted to evaluate the interaction of colestipol and atorvastatin. One hundred and six patients with hypercholesterolemia, males and females, were randomly assigned to an open-label, multicenter 12 week study evaluating atorvastatin and colestipol in combination and separately. Ten mg of atorvastatin was given once daily alone or with 20g/day (BID) of colestipol. The mean percent decrease in LDL-C was as follows: 45% atorvastatin-colestipol combination, 35% atorvastatin and 22% colestipol alone. Atorvastatin was better tolerated than colestipol as either mono- or combination therapy because of the GI side effects.

The second study was a 52 week open-label, parallel-arm study with 469 patients designed to compare 80 mg atorvastatin to colestipol alone, and colestipol in combination with either 40 mg simvastatin or 40 mg atorvastatin. After 16 weeks, LDL-C decreases were 54% for atorvastatin and 16% for colestipol . At week 52, LDL-C decreases were 53% for atorvastatin-treated patients, 46% for simvastatin+colestipol treated patients and 53% for the atorvastatin+colestipol combination. This study compared to the first indicates that increasing the dosage of atorvastatin increases its effectiveness and that the 80 mg atorvastatin yields the same level of effectiveness

as the colestipol+ atorvastatin 40 mg combination.

VII. Population Pharmacokinetics

Plasma atorvastatin equivalent concentrations were collected from 444 patients (853 samples collected 8 to 16 hour postdose) who participated in 2 clinical efficacy and safety trials. A linear mixed effect model was fit to the atorvastatin-equivalent concentration data. Time of sample collection was ignored.

$$\overline{Cp_{ij}} = \theta_1 \cdot \theta_2^{D40ij} \cdot \theta_3^{D80ij} \cdot \theta_4^{SEXj} \cdot \theta_5^{RACEj} \cdot \theta_6^{DDIij} \cdot \theta_7^{AGEj} \cdot \theta_8^{BMIj}$$

where $\overline{Cp_{ij}}$ is the typical concentration predicted in the j^{th} individual at the i^{th} dose and

D40	1 if 40 mg dose, 0 otherwise
D80	1 if 80 mg dose, 0 otherwise
SEX	1 if male, 0 if female
RACE	1 if other than Caucasian, 0 if Caucasian
DDI	1 if colestipol coadministered, 0 otherwise
AGE	1 if patient over 49 years old, 0 otherwise
BMI	1 if patient over 25 kg/m^2, 0 otherwise

Three-fourths of the data encompassed values obtained from the 40 and 80 mg dosages. A 481 and 25 point drop in objective function was observed due to dosage and colestipol coadministration, respectively. These were the only two covariates that impacted the model. Simple 1- and 2- compartment pharmacokinetic models were unacceptable due to the high degree of "noise" in the atorvastatin-equivalent concentration time profile during the 8 hour collection interval.

The linear mixed effect model used to fit the atorvastatin equivalent concentration data without regard to time of sample collection was appropriate, considering the long half life associated with the 8 to 16 h postdose interval. Samples were collected at weeks 4, 8 and 16 (i.e. steady-state). However, the model was not validated. Although colestipol did improve goodness-of-fit by lowering the objective function by 25 points (a significant decrease stipulated as a log-likelihood difference (LLD) of 20 points) it did not affect variability in concentration.

In regards to ethnicity, the sponsor did not have an adequate sample size of black patients (3.2%) to draw any meaningful conclusions in the sparsely sampled patient data formal analysis. The sponsor then presented a histogram (Figure 9) which overlayed AUCs for 25 black healthy subjects (7.5% of the database) and compared them to the total number of subjects and inferred no differences in AUC based on visual inspection. This data was obtained from various single and multiple dose studies . Since no formal analysis was performed on the healthy black subjects and due to the sample size, the sponsor has not adequately studied the effect of race.
This study clearly demonstrated that dosage was the only variable to impact atorvastatin

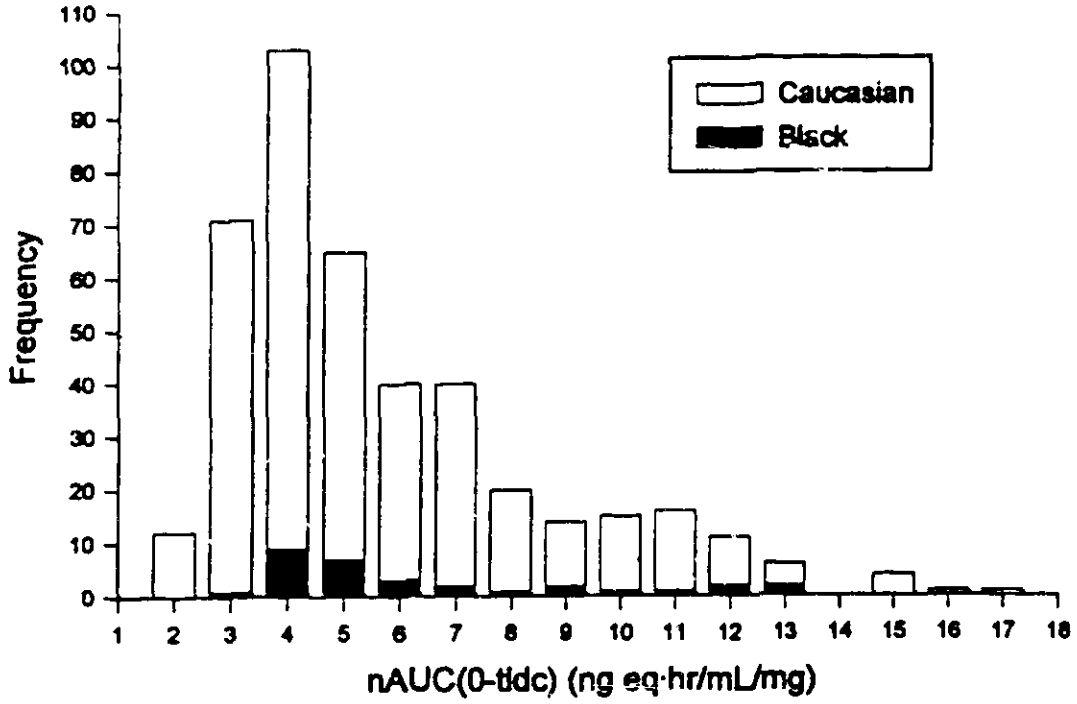


Figure 9: Effect of storvastatin equivalent AUC values in blacks determined in selected clinical pharmacology studies

VIII. Pharmacodynamic Assessment

The primary efficacy parameter was the mean percent change from baseline in LDL-C estimated by use of Friedewald's formula. Secondary efficacy parameters evaluated mean percent changes from baseline in total cholesterol, triglycerides, HDL-C, L[illegible]-C (β-Quant) and Apolipoproteins A1 and B and lipoprotein(a). A double-blind, placebo controlled once daily dose ranging

A I and B and lipoprotein(a). A double-blind, placebo controlled once daily dose ranging (placebo, 2.5, 5, 10, 20, 40, 80 mg) safety and efficacy trial was conducted over 6 weeks using the amorphous form. This study was repeated as a nonblind, placebo-controlled once daily 6 week dose ranging (placebo, 10, 20, 40, 60 80 mg) safety and efficacy trial using the crystalline form of the drug. The ability of the two forms to lower LDL-C, Total cholesterol and Apo B was comparable (see Table 9). The decrease in these parameters was dose related. In the crystalline trial, LDL-C decreased 37%, 42%, 50%, 52% and 59% for patients receiving 10mg, 20mg, 40mg, 60mg and 80mg atorvastatin, respectively. The mean increase for the placebo group was 0.3%. No appreciable lowering of Apo A was achieved. By the 2nd week of the study, a significant mean change from baseline was observed and maintained throughout the study period. A dose related increase in the number of patients (11 total, representing 15% of study population) experiencing an increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels was observed. This increase was observed at the 40mg level and continued with increasing dosage. This increase in enzyme levels was not observed in the study in which subjects were administered the amorphous form. Only 1 patient (1% of study population) experienced elevated ALT and AST.

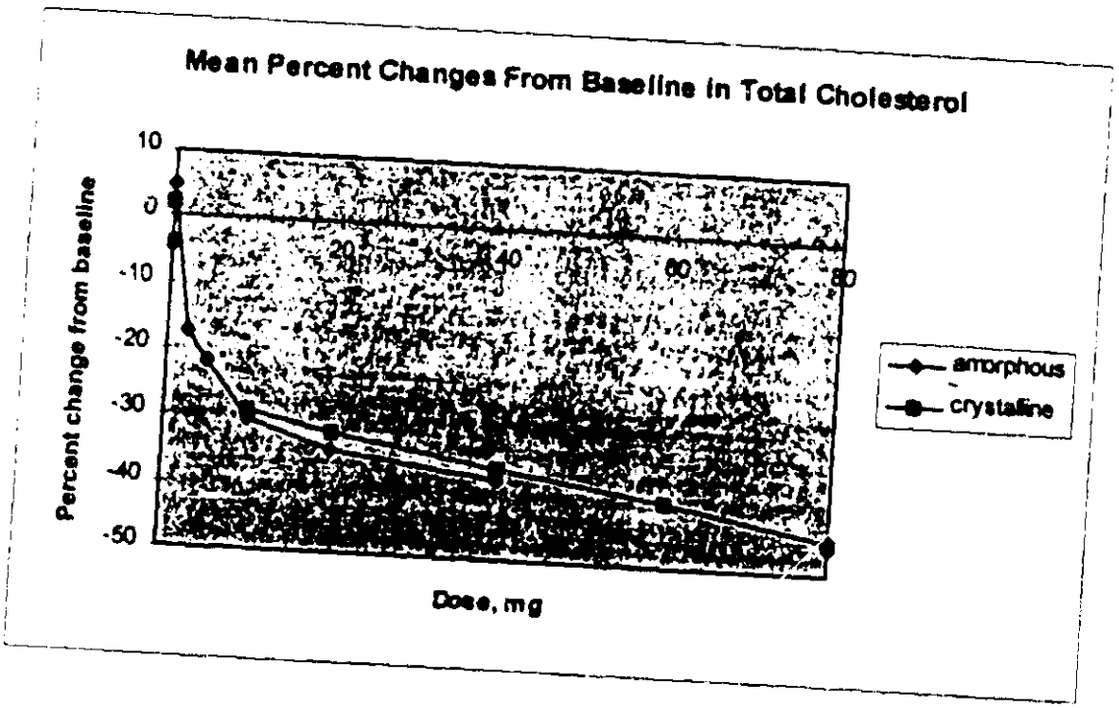


Figure 10: Mean percent changes from baseline in total cholesterol vs. formulation

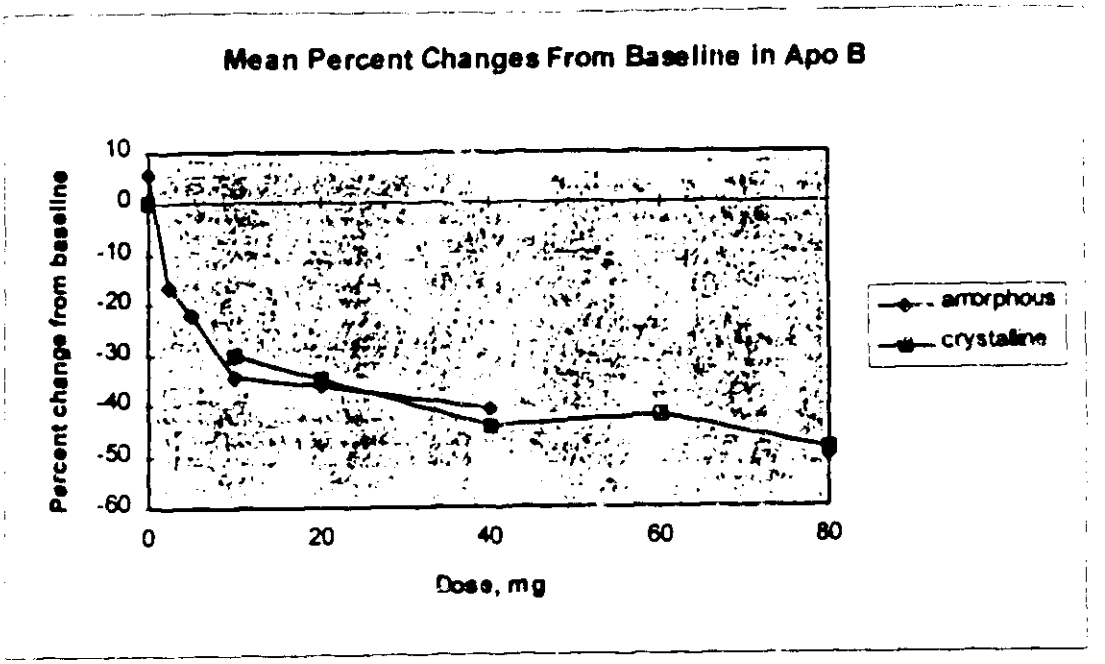


Figure 11: Mean percent changes from baseline in Apo B vs. formulation

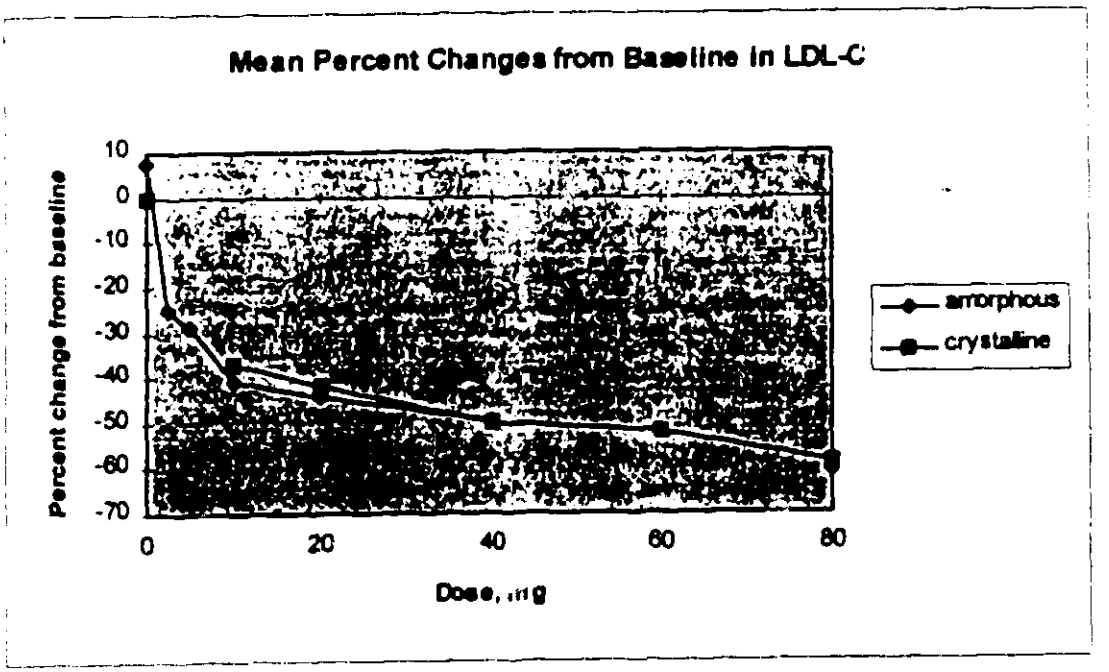


Figure 12: Mean percent changes from baseline in LDL-C vs. formulation

TABLE 11. COMPARISON OF MEAN (SE) VALUES FOR PRIMARY AND SECONDARY EFFICIENCY PARAMETERS OBTAINED IN TWO 6 WEEK SAFETY AND EFFICACY TRIALS USING EITHER THE AMORPHOUS OR THE CRYSTALLINE FORM OF ATORVASTATIN

Variable	Placebo N=12/9	2.5mg N=11	5.0mg N=13	10mg N=11/11	20mg N=10/10	40mg N=11/10	60mg N=13	80mg N=11/12
Primary Parameter	PERCENT CHANGE							
LDL-C, mg/dL	+7.6/ 0.0	-25.0	-29.0	-41.0 / -37.0	-44.0/-41.0	-49.7/ -50.0	-52.0	-61.0/ -59
Secondary Parameters								
Total Cholesterol, mg/dL	+4.8/ +2.0	-17.3	-21.8	-30.3/ -29.0	-34.5/ -32.0	-37.8/ -36.0	-40.0	-45.7/ -45.0
Apo B, mg/dL	+5.8/ 0.0	-16.6	-21.9	-34.4/ -30.0	-36.3/ -35	-40.9/ -44.0	-42.0	-50.3/ -49.0
Triglycerides, mg/dL	+26.0			-27.0	-23.0	-33.0	-37.0	-45.0
HDL-C, mg/dL	-3.0			+8.0	+8.0	+13.0	+3.0	+7.0
Apo A-1	-5.0			-1.0	+2.0	+2.0	-7.0	-7.0

IX. Pharmacokinetic/Pharmacodynamic Relationship

A multiple-dose study of healthy subjects with raised cholesterol levels was conducted using the amorphous form of atorvastatin to evaluate the PK/PD relationship and dose proportionality. Subjects were given 5, 20 and 80 mg doses of atorvastatin QD for 6 weeks. Percent decrease in LDL-C cholesterol and atorvastatin dose is log-linear with the individual dose-response curves parallel to the mean dose-response curve. Individual rank ordering of responses was maintained across doses for $AUC_{(0-24)}$, C_{max} and C_{min} values. There was no relationship between AUC and LDL-C reduction. Patients who had large AUCs relative to others did not exhibit larger reductions in LDL-C. Furthermore, at 80 mg, reductions in LDL-C response were not accompanied by reductions in variability of $AUC_{(0-24)}$.

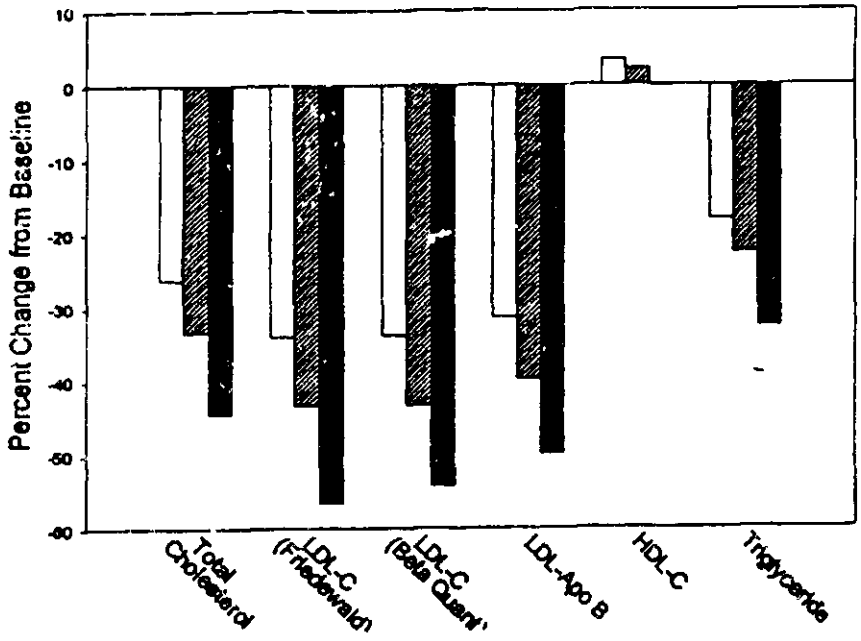


Figure 13: Least-squares mean values for percent change fom baseline in lipids following administration of 5 (Open Bar), 20 (Shaded Bar), and 80 (Closed Bar) mg Atorvastatin QD for 6 weeks to subjects with elevated cholesterol levels

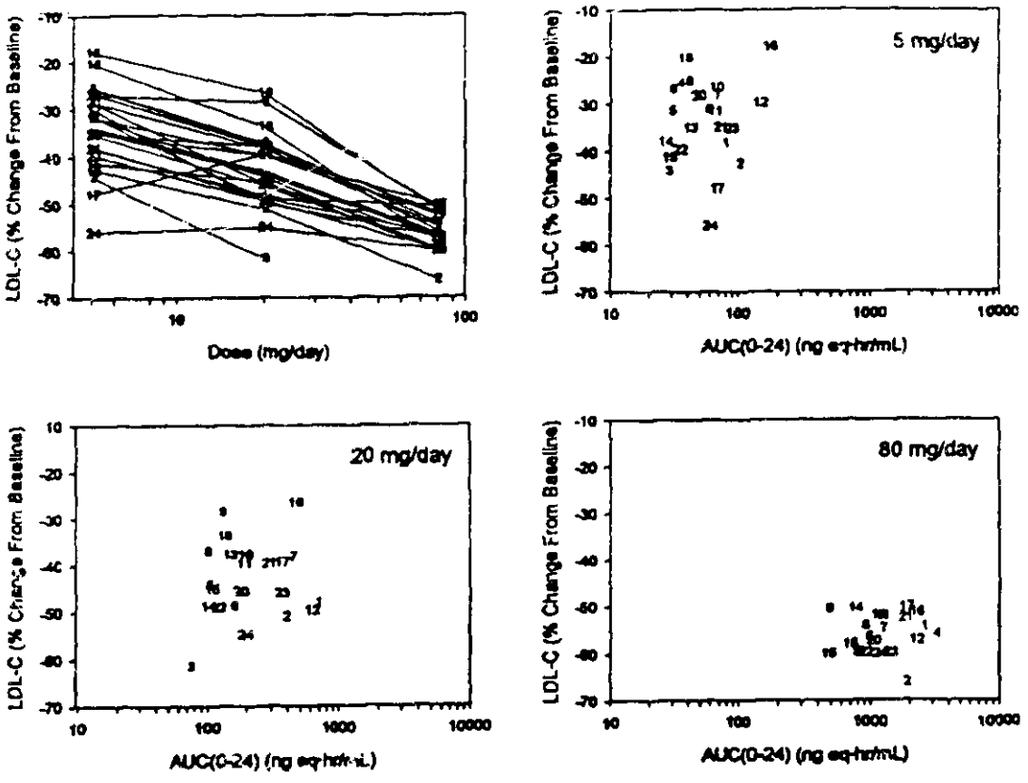


Figure 14: Relationships between percent change of LDL-C (Friedewald) from baseline and log-transformed dose and atorvastatin-equivalent AUC(0-24) values at different dose levels

General Comments (to be sent to the sponsor)

1. An inappropriate study design was used for the evaluation of bioequivalence. In situations where both the parent drug and metabolite(s) are active, all active entities should be tested for bioequivalence. In the case of atorvastatin, C_{max} is statistically higher in the crystalline tablet compared to the amorphous tablet. A repeat of these studies using the active metabolites may yield a greater magnitude of difference in C_{max} and possibly indicate statistical significance in AUC which is not currently being observed.

2. The sampling scheme in many of the studies including the bioequivalence studies was not adequate. In most cases the first collection time point was at 0.5 hours. In some of the studies the drug had already reached its C_{max} at this time point. In some of the trials reviewed this phenomenon was noted in 50% of the subjects. Therefore, the C_{max} values will be higher than what was reported.

3. The sponsor did not adequately characterize the metabolic products. The company should determine the routes of metabolism for the two active metabolites and their respective binding capacities.

4. When conducting drug interaction studies, the drug interaction should be studied in both directions i.e., the effect of the reference compound on the test drug's pharmacokinetics and the effect of the test drug on the reference drug's pharmacokinetics.

5. Although water is not usually recommended as a dissolution medium by the Office of Clinical Pharmacology and Biopharmaceutics it is being recommended on an interim basis for this product. However, the sponsor should attempt to find a better dissolution medium since water has a lack of buffering capacity. The pH of water may vary before and after dissolution testing which may affect the solubility/dissolution of the product.

Labeling Comments

1. (p. 10) Sixth sentence should be changed to, " Food decreases... as assessed by C_{max} and AUC. LDL-C reduction is similar whether atorvastatin is given with or without food, however, an increase in adverse events is observed in the absence of food."

The last sentence should be changed to, "LDL-C ...drug administration, however, an increase in adverse events is observed with morning administration."

1. (p. 13) The statement "Race: ..." should be deleted.

This change is suggested because the sponsor has not adequately demonstrated similarity in the pharmacokinetics of atorvastatin between black and white subjects. Although a population pharmacokinetic analysis was performed, black patients represented 3% of the database. In the visual inspection of a frequency distribution histogram generated from a population that included 7% black healthy volunteers, the same problem of lack of adequate sample size existed. This drug will most likely be used in high proportions in minority groups. Therefore, pharmacokinetic characterization in blacks and other minorities is very important.

2. (p. 14) Add after the words "chronic alcohol liver disease" the following: "...and C_{max} and AUC are 4-fold greater for the Childs-Pugh A group."

Addition of this statement is suggested so readers of the label are aware that the Childs-Pugh A rating also has a significant impact on the pharmacokinetics of atorvastatin.

3. (p. 31) Add after the first sentence in the section on cimetidine drug interaction the following: "However, cimetidine appears to significantly prolong half-life (17 h vs. 10 h). Patients should be monitored appropriately for accumulation."

This change is suggested because the company could not provide a reasonable explanation for this prolongation of half-life.

4. (p. 44) Second paragraph, third sentence should be changed to read, "...as a single dose in the evening with a meal."

This suggestion is being made to possibly lessen the occurrence of toxicity, without diminishing the pharmacodynamic performance of atorvastatin. The two formulations of atorvastatin are not bioequivalent and the crystalline form is significantly more potent as evidenced by the higher C_{max}. Toxicity is a concern. The diurnal study indicates that a reduction in C_{max} and AUC is observed during evening administration of atorvastatin compared to the morning. Furthermore, food effect studies indicate a reduction of C_{max} in the presence of a meal.

Carolyn D. Jones

Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics
9/10/96

RD initialed by Hae-Young Ahn, Ph.D., Team leader 9/26/96

Clinical Pharmacology and Biopharmaceutics Briefing (10/22/96, Huang, Strong, Fleischer, Ahn, Mehta, Shore, Chen)

FT initialed by Hae-Young Ahn, Ph.D., Team leader 10/25/96

NDA 20-702 (1 copy), HFD-510(Orloff, RheeJ), HFD-340 (Vishwanathan), HFD-850 (Lesko), HFD-870(Ahn, Jones and M. Chen), HFD-870(Drug file, Chron. file, Reviewer).

NOV 18 1996

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 20-702 **CHEMISTRY REVIEW #:** 2 **DATE REVIEWED:** 18-NOV-1996

Submission Type	Document Date	CDER Date	
Original	17-JUN-1996	17-JUN-1996	**User fee I.D. Nº 2566**
Amendment	08-NOV-1996	12-NOV-1996	
Amendment	15-NOV-1996	18-NOV-1996	

NAME & ADDRESS OF APPLICANT: Parke-Davis, Pharmaceutical Research Division
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105 (313) 996-5185

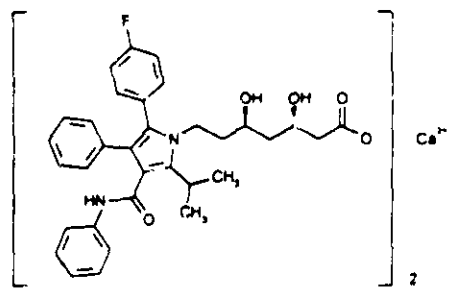
DRUG PRODUCT NAME Proprietary: Lipitor
Nonproprietary/Established/USAN: Atorvastatin Calcium
Code Name(s) CI-981 Calcium, PD 134298-38A
Chem. Type/Ther. Class: **1 P**

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

DOSAGE FORM: Tablets **STRENGTHS:** 10, 20 and 40 mg

ROUTE OF ADMINISTRATION: Oral **DISPENSED:** R

CHEMICAL NAME/ STRUCTURAL FORMULA:



$(C_{33}H_{34}FN_2O_5)_2Ca$
FW = 2 x 557.7 + 40.0 = 1155.38 (anhydrous calcium salt)

FW calcium salt trihydrate $(C_{33}H_{34}FN_2O_5)_2Ca \cdot H_2O$ = 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)

COMMENTS: This amendment provides the applicant response to the CMC deficiencies delineated in the Agency correspondence dated November 6, 1996.

CONCLUSIONS & RECOMMENDATIONS: The application can be approved from the Chemistry viewpoint **pending an acceptable decision for the manufacturing facilities with respect to cGMP compliance** by the Division of Manufacturing and Product Quality Control. Parke-Davis commits to

Orig. NDA 20-702
cc: HFD-510/Division File
HFD-510/BarbehennE/MooreS/OrloffD/RheeJ/YsemX
HFD-820/GibbsJ

Xavier Ysern, PhD

R/D Init by: **filename:** 20702_2.nda

Stephen K. Moore 11/18/96

NOV - 5 1996

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 20-702 **CHEMISTRY REVIEW #:** 1 **DATE REVIEWED:** 4-NOV-1996

Submission Type	Document Date	CDER Date	
Original	17-JUN-1996	17-JUN-1996	**User fee I.D. Nº 2566**

NAME & ADDRESS OF APPLICANT: Parke-Davis, Pharmaceutical Research Division
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105 (313) 996-5185

DRUG PRODUCT NAME

Proprietary:	Lipitor
Nonproprietary/Established/USAN:	Atorvastatin Calcium
Code Name(s)	CI-981 Calcium, PD 134298-38A
Chem. Type/Ther. Class:	**1 P**

PATENT STATUS: U.S. Patent Nº 4,639,436 (drug, drug product, method of use) to Bayer AG. Exp. 27-JAN-2004

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

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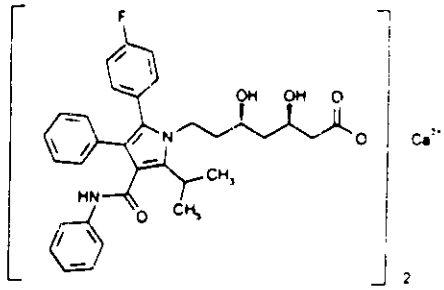

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CONCLUSIONS & RECOMMENDATIONS: The application is **approvable** from the Chemistry viewpoint **pending a favorable Environmental Assessment evaluation, acceptable decision for the manufacturing facilities with respect to cGMP compliance** by the Division of Manufacturing and Product Quality, **and satisfactory response to the deficiencies** letter.

Orig NDA 20-702
cc HFD-510/Division File
HFD-510/BarbehennE/MooreS/OrloffD/RheeJ/YsernX
HFD-820/ChiuY-Y/GibbsJ

Xavier Ysern, PhD

R/D Init by

Stephen K. Moore 11/5/96

filename: 20702_1.nda

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dr. Daniel Boring, Chair, HFD-530, Corporate Building, Room N461

From: Division of Metabolism and Endocrine D. P./ HFD-510
Attention: Dr. Xavier Ysern Phone: (301) 443-3510

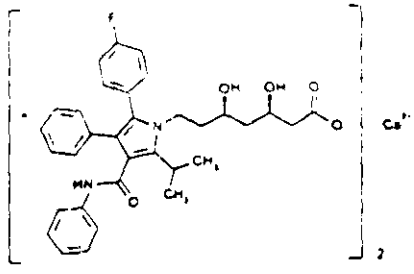
Date: 26-FEB-1996

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Lipitor

IND #: 35,544

Established name, including dosage form: Atorvastatin Tablets



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Other trademarks by the same firm for companion products: - N.A. -

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 (303) 996-7000

Indications for Use (may be a summary if proposed statement is lengthy):

Lipid Modifier, Antihyperlipoproteinemic agent.

Initial comments from the submitter (concerns, observations, etc.):

Parke Davis Pharmaceutical Research plans to present a NDA submission for the antihyperlipoproteinemic agent atorvastatin tablets early summer (June) 1996.

filename: 35544.tm

NOTE: *Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible*

Rev Oct. 1993

3/6 76

Consult #560 (HFD-510)

LIPITOR atorvastin tablets

The Committee found no look alike/sound alike conflicts or misleading aspects in the proposed proprietary name.

The Committee has no reason to find the proposed trademark unacceptable.

T W Koerner 4/4/96, Chair

CDER Labeling and Nomenclature Committee

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Lipitor™
(Atorvastatin Calcium)
Tablet
NDA 20-702

Warner-Lambert/Park-Davis

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Metabolic & Endocrine Drug Products
(HFD-510)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-702

Lipitor™

(Atorvastatin Calcium)

Tablet

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that it will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Lipitor™, Warner-Lambert has prepared an environmental assessment (attached) in accordance with *21 CFR 25.31a(a)*, which evaluates the potential environmental impact of the manufacture, use and disposal of the product. The maximum expected environmental concentration is at a level that normally relieves the applicant from completing format items 7, 8, 9, 10, 11, and 15 in accordance with the Tier 0 approach specified in the *Guidance for Industry for the submission of an Environmental Assessment in Human Drug Applications and Supplements*.

Atorvastatin calcium, chemically synthesized drug, is administered in the form of a tablet, as an adjunct to diet to reduce elevated total and LDL-C levels in patients with primary hypercholesterolemia (type IIa), when the response to a diet restricted in saturated fat and cholesterol is inadequate. The drug substance is manufactured by Parke-Davis Holland Chemical Division, Holland, Michigan, and Warner-Lambert Plaistow Facility, County Cork, Ireland. The drug product is manufactured by Warner Chilcott Laboratories, Lititz, Pennsylvania and Goedecke AG, Freiburg, Germany. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Atorvastatin calcium may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Drug substance and product that fail specification, pass expiration period, or are returned from the field are destroyed by high temperature incineration by approved and regulated facilities. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

10/31/96
Date

CONCURRED
Nancy [illegible]ger
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

10/31/96
Date

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet (drug substance)

FONSI for NDA 20-702

ITEM 3.6.
Freedom of Information Environmental Assessment

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ENVIRONMENTAL ASSESSMENT

(Freedom of Information Environmental Assessment Information)

Environmental Impact Analysis Report

This report was prepared following the guidelines issued November 1995 by the Center for Drug Evaluation and Research titled *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements*. We have calculated in Section 3.5.6 that the expected environmental concentration of the drug substance is 0.43 ppb, which is less than the threshold of 1 ppb. We have, therefore, omitted the following sections from this report:

- 7, Fate of Emitted Substances in the Environment;
- 8, Environmental Effects of Released Substances;
- 9, Use of Resources and Energy;
- 10, Mitigation Measures;
- 11, Alternatives to the Proposed Action; and
- 15, Summary Tables.

3.6. Environmental Assessment - Atorvastatin 10-, 20-, and 40-mg Tablets

3.6.1. Date

Prepared: April 1, 1996
Revised: October 25, 1996

3.6.2. Name of Applicant

Warner-Lambert Company

3.6.3. Addresses

Corporate Address

201 Tabor Road
Morris Plains, NJ 07950

Division Address

Warner-Lambert/Parke-Davis
Pharmaceutical Research Division
2800 Plymouth Road
Ann Arbor, MI 48105

3.6.4. Description of the Proposed Action

3.6.4.1. Requested Action

Warner-Lambert has filed a New Drug Application for atorvastatin 10-, 20-, and 40-mg tablets. The drug substance is atorvastatin calcium. The New Drug Application requests approval of atorvastatin tablets as an adjunct to diet to reduce elevated total and LDL-C levels in patients with primary hypercholesterolemia (Type IIa) including heterozygous and homozygous familial hypercholesterolemia, and combined hyperlipidemia (Type Ib) when the response to a diet restricted in saturated fat and cholesterol is inadequate.

3.6.4.2. Need for Action

Approval of this application will result in production and distribution of atorvastatin 10-, 20-, and 40-mg tablets. Approval will offer patients in the United States an alternative treatment for hypercholesterolemia and hyperlipidemia when the response to a diet restricted in saturated fat and cholesterol is inadequate. Because of the benefits associated with an alternative treatment for hypercholesterolemia and hyperlipidemia, approval is sought and preferable to nonapproval. The Indications and Usage Section

for Proposed Package Insert for this product is provided in Appendix 1. The Material Safety Data Sheet for atorvastatin calcium is provided in Appendix 2.

It is estimated that there are currently 4 million patients in the United States who would benefit from cholesterol and lipid reduction. Estimates of the quantity of atorvastatin to be produced have been determined from 5-year market forecasts for this product considering the appropriate patient population and dosing regimens requested in the labeling.

3.6.4.3. Sites of Production

Bulk drug substance will be manufactured, tested, and released at the following Warner-Lambert facilities:

Parke-Davis Holland Chemical Division (Holland Facility)
Warner-Lambert Company
188 Howard Avenue
Holland, MI 49424

and

Warner-Lambert Plaistow Manufacturing Partnership (Plaistow Facility)
Little Island Industrial Estate
Wallingstown
Little Island
County Cork
Ireland

Drug substance intermediate [redacted] will be manufactured by either the Parke-Davis Division of the Warner-Lambert Company, Newport Synthesis LTD, or ISP Fine Chemicals Inc at the locations listed below.

Parke-Davis Division
Warner-Lambert Company
188 Howard Avenue
Holland, MI
USA, 49424

Newport Synthesis LTD
Baldoyle Industrial Estate
Grange Road, Baldoyle
Dublin, Ireland

ISP Fine Chemicals Inc
1979 Atlas Street
Columbus, OH
USA, 43228

Drug substance intermediate [redacted] of atorvastatin ([redacted]) will be manufactured by the Parke-Davis Division of the Warner-Lambert Company or Wacker-Chemie GmbH at the locations listed below.

Parke-Davis Division
Warner-Lambert Company
188 Howard Avenue
Holland, MI
USA, 49424

Wacker-Chemie GmbH
Werk Burghausen
8263 Burghausen/Obb.
Germany

Drug product manufacturing, packaging, testing, and release will be performed at the following Warner-Lambert facilities:

Warner Chilcott Laboratories (Lititz Facility)
Warner-Lambert Company
400 West Lincoln Avenue
Lititz, PA 17543

and

Goedecke AG
Werk Freiburg
Mooswaldallee 1
D-79090 Freiburg I/Br
Germany

Alternatively, drug product blister packaging may be performed at the following contract packaging facility:

Paco Packaging Inc
1200 Paco Way
Lakewood, NJ 08701

3.6.4.4. Environmental Settings of Domestic and Warner-Lambert Manufacturing Locations

The environmental settings of the Warner-Lambert drug substance and drug product manufacturing and packaging facilities are as follows:

3.6.4.4.1. Parke-Davis Holland Chemical Facility

The Parke-Davis Holland Chemical facility is located on approximately 50 acres of land in the Township of Holland (1990, Population 17,523), in Ottawa County, Michigan, approximately 30 miles west of Grand Rapids. The site consists of

approximately 15 buildings and employs an average work force of 300 employees. It is adjacent to the Macatawa River near the river's confluence with Lake Macatawa. Lake Macatawa flows into Lake Michigan approximately 4.5 miles downstream from the facility. The plant is located in an industrial and commercial area in which the surrounding neighborhood includes residential, light industry, retail business, and beech-maple forests. The site is just north of the city of Holland.

Air Resources

Ambient air quality at this facility is not routinely monitored. Indoor air quality is monitored. The facility has an air quality permit for its thermal oxidation system. Approval of this product will not exceed permit limits. The facility has a number of other air permits that are not associated with hazardous waste management but are associated with the specific batch manufacturing processes conducted at the site. Air emission permit applications have not been submitted and approved for the individual steps of the atorvastatin calcium manufacturing processes. An analysis of the emissions from the manufacturing process for atorvastatin and its intermediates has determined that the air emissions are negligible and do not require the submission of air permit applications. This analysis has been communicated to the Michigan Department of Environmental Quality (MDEQ).

Water Resources

The Holland facility receives its potable water from Holland Township. Holland Township obtains its potable water from the city of Wyoming, the city of Holland, and in rural areas, from ground water. Wyoming obtains water from Lake Michigan via an intake structure located approximately 6 miles northwest of the facility and about 6 miles north of Lake Macatawa's outlet to Lake Michigan. The city of Holland obtains its potable water from Lake Michigan via an intake located about 0.75 miles off-shore and about 5 miles west of the facility and 2 miles north of Lake Macatawa's outlet to Lake Michigan. The facility pumps its sanitary wastes to the Holland Municipal Waste Treatment Facility.

Process water for noncontact cooling is obtained from an intake located on the channel leading to the Macatawa River on the east side of the facility. This noncontact cooling water is combined with the treated sanitary wastes and treated process wastes and discharged into the Macatawa River under NPDES Permit MI 0004715 (expires 10/01/96[a]). Approval of this product will not exceed permit limits.

A storm water retention pond is located in the southwest corner of the site next to the Macatawa River. This pond receives surface runoff from the west part of the site, except runoff from certain roofs and all secondary containment areas which is sent to the chemical waste treatment system. The unlined retention pond has no outlet, but water leaves it through the soil. Water from this treatment system is disposed of by deepwell injection for which Permits MI-139-1W-0003, MI-139-1W-0004, and MI-139-1W-0005 (expires 08/14/97) have been granted. Approval of this product will not exceed permit limits.

Land Resources

The Holland facility is located on a former beach and associated offshore deposits of a higher stage of Lake Michigan. These areas have locustrine sand and gravel deposits and may include intercalated clay. Eolian sand and organic soils may be present. The area is in the Eastern Deciduous Forest Ecoregion, and the climax forest is beech-maple (Bailey Robert G., 1978). The site slopes from a high in the north of 605 feet to the Macatawa River in the south, which has an approximate elevation of 579 feet. The site is mostly paved or covered by buildings.

Environmental Regulations

Air emissions are regulated by Michigan Act 348. Due to the batch nature of the facility operations, the agency (previously the Michigan Department of Natural Resources - MDNR and currently the Michigan Department of Environmental Quality - MDEQ) issues air emissions control permits for entire manufacturing operations. Air

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[a] Application for new NPDES permit submitted on 03/29/96. MDEQ allows operation under current permit until new one is granted

emission permit applications have been determined to not be required for the atorvastatin calcium process and this request has been provided in writing to the Michigan Department of Environmental Quality.

The Thermal Oxidizer has been granted approval prior to the manufacture of this product. The Thermal Oxidizer has been granted 923-85. Approval of this product will not exceed the limits for these permits.

Aqueous emissions are regulated by Michigan Minerals Wells Act. Safe Drinking Water Act, Clean Water Act, and the Resource Conservation and Recovery Act. Compliance with these statutes has been achieved by obtaining Underground Injection Control permits from US EPA MI-139-1W-0003, MI-139-1W-0004, and MI-139-1W-0005. For cooling water discharges, NPDES Permit MI 0004175 has been granted. Approval of this product will not exceed the limits for these permits.

Treatment and storage of hazardous wastes are regulated by Michigan Act 64 and the Resources Conservation and Recovery Act. Michigan Act 64 License 006013643 (expires 10/29/95)[b] has granted.

Off-site disposal of hazardous waste is performed in accordance with Michigan Act 64, Resource Conservation and Recovery Act, and the Hazardous Materials Transportation Act regulatory requirements. The State Historic Preservation Officer of Michigan has determined that the property does not require a historic property evaluation for installation of new equipment.

Warner-Lambert certifies that the Holland Chemical Facility is in compliance with permit limits and environmental regulations. A letter of certification is provided in Appendix 4.

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[b] Application submitted to MDEQ on 04/15/95. Application revised 08/01/95. MDEQ allows operation under current permit until new one is granted.

3.6.4.4.2. Plaistow Chemical Facility

The Plaistow bulk pharmaceutical manufacturing facility is located on approximately 12 acres of land in the town of Wallingstown in the parish of Little Island, County Cork. The site contains 6 buildings and employs an average work force of 65 employees. The site is situated on the Little Island Industrial Estate which was developed by the Industrial Authority. The estate was zoned for industrial use, particularly capital intensive industry with significant water usage. Plaistow purchased 10 acres of land at Wallingstown, Little Island in 1976 and an additional 2 acres adjoining the site in 1995. The site is approximately 0.5 km from Cork Harbour. The site is relatively flat with a level approximately 9 meter ordinance datum.

Air Resources

The site has an air emission license, AP 16/89 issued by the local authority, Cork County Council under the 1987 Air Pollution Act. Indoor air quality is monitored in the production buildings.

Water Resources

The Plaistow facility receives its water from the Glashaboy and Iniscarra water treatment plants of the Cork County Council. The potable water complies with the EC Quality of Water Fit for Human Consumption Regulations. There is an ion-exchange facility on-site for treating process water.

Process waste water and storm water from bonded storage areas is treated in the on-site activated sludge waste water treatment plant. The discharge is licensed by Cork County Council under the 1977 Water Pollution Act. Uncontaminated cooling water along with storm water runoff is discharged directly to a tidal basin under the same permit.

Land Resources

The Plaistow facility is located in the townland of Wallingstown in the northwestern portion of Little Island. The site is underlain by Waulsortian limestone bedrock covered by a layer of glacial deposits. The glacial deposits consist of firm to stiff brown sandy silt with gravel. Occasional sandy and gravelly lenses occur within the till and the overburden is typically 10 meters thick. The site is relatively level and is approximately 30% paved or covered with buildings.

Environmental Regulations

Air emissions are regulated by the 1987 Air Pollution Act and the site has been granted air emission permit AP 16/89. Aqueous emissions are regulated by the 1977 Water Pollution Act and subsequent amendments. The site has been granted a discharge permit WP(W) 12/83. Off-site disposal of general trade waste and activated sludge to local authority landfills is carried out by a contractor licensed under the 1979 Waste Act. Off-site disposal of hazardous waste for recovery or incineration is performed by licensed contractors in accordance with the EC Hazardous Waste Regulations.

Plaistow Limited Manufacturing Chemists Inc certifies that the Plaistow Chemical Facility is in compliance with permit limits and environmental regulations in Ireland. A letter of certification is provided in Appendix 5.

3.6.4.4.3. Lititz Drug Product Facility

The Warner-Lambert Lititz facility is located in the Borough of Lititz, Lancaster County, Pennsylvania. It is located approximately 60 miles west of Philadelphia and 7 miles north of Lancaster in south-central Pennsylvania. The borough covers 2.2 square miles and has a population of 8,280 people (1990 Census).

The facility is located on approximately 87 acres. The original building was constructed in 1956 with additional construction in 1966, 1981, 1989, and 1992. The total square footage of the facility is approximately 1.1 million square feet

The land use immediately adjacent to the facility is varied. North and east of the site are commercial manufacturing facilities. To the southeast is a borough park. Land south and west is owned by the local school district which contains schools and recreation facilities. Farm land is located directly west of the facility.

The land use of the borough is approximately 75% residential and agricultural, 15% commercial and industrial, and 10% public.

Air Resources

Manufacturing operations are issued permits by the Pennsylvania Department of Environmental Protection (PA DEP). The air permits issued to the Lititz facility are for dust collection equipment which is used in the weighing, milling, blending, mixing, tablet compression, tablet coating, and packaging operations employed in the manufacture of tablets. Approval of atorvastatin tablets will not result in the exceedance of allowable permit limits.

Water Resources

The Warner-Lambert Lititz facility receives its potable water from the Lititz Borough Water Authority. The Lititz Borough pumping station pumps approximately 1.25 million gallons of water per day from 6 wells. Water is drawn from the Lititz Borough Water Authority distribution system into the Lititz facility. The water to be used for pharmaceutical product manufacture undergoes treatment via a deionization and ozonation system.

All waste water, including the water from the cleaning of manufacturing equipment, is discharged into the Lititz Borough Waste Water System which is processed at the Lititz Borough Waste Water Pretreatment Plant. The effluent discharged into the waste water system is regulated under the Borough of Lititz Code, Chapter 100. The Borough of Lititz does not issue permits but does require industrial users to monitor their discharges quarterly for contaminants described in the Code. Monitoring reports are submitted to the Borough of Lititz quarterly. Waste water from the Lititz site is

also regulated by the US EPA under the requirements of 40 CFR Part 439 (D). The monitoring requirements for the Lititz site are specified in Permit Number PAP120320. The approval of this application will not result in the exceedance of permit limits.

Land Resources

The topography of Lititz is flat to gently rolling with the flatter areas in the west of town. Elevations in the area vary from 350 to 450 feet above sea level. The slope of the Lititz Manufacturing Site varies from a topographic height of 400 feet above mean sea level in the northeast corner and gently slopes to a low of 375 feet in the southeast corner.

The borough of Lititz is underlain by the Epler and Stonehenge formations of the Ordovician Age (USGS). The Eppler formation is a light gray, fine-grained limestone with thin interbeds of light gray dolomite. The Stonehenge formation located to the south of the facility is a medium gray limestone with dark gray interbeds of silty limestone and some conglomeric materials. The contact between the 2 formations run east to west across the southern boundary of the facility. Both the Epler and Stonehenge formations are known for sinkholes. The Lititz facility has expended considerable resources into sinkhole management and prevention.

The soils at the site correspond to the Hagerstown silt loam series (United States Department of Agriculture Soil Conservation Service). The soils are reported to be deep and well-drained. The surface layer is typically dark-brown silt loam approximately 10-inches thick, with the subsoil of yellowish-red silty clay loam in the upper layer, to a strong brown silty clay and silty clay loam in the lower layers extending to a depth of 60 or more inches. The available water capacity is high and runoff is medium.

Environmental Regulations

Air emissions are regulated by the Pennsylvania Department of Environmental Protection (PA DEP). The applicable regulations are under the Pennsylvania Code, Title 25, Part 1, Subparta C, Article III, Chapters 121 to 143. Chapter 123 of the

Pennsylvania Code specifies sources exempt from permit requirements or permitted by rule. All sources not exempted by the PA DEP must apply for a permit exemption or permit, and the PA DEP will determine the permit requirements. Sources not receiving a written exemption from the PA DEP must file a Plan Approval with the PA DEP prior to the purchase and installation on emission control equipment. The PA DEP issues a Plan Approval and a Temporary Operating Permit. A Temporary Operating Permit will allow operation of the source emissions for not more than 180 days. If the 180-day period is to be exceeded, the facility must submit a written request for an extension of the Temporary Operating Permit. The PA DEP will issue an operating permit after a satisfactory inspection of the emission source.

Water discharges are regulated by the Lititz Borough Sewer Authority and the US EPA. The facility does not currently treat waste water discharges on-site. Treatment is performed by the Borough of Lititz Waste Water Treatment Plant. The US EPA regulates waste water discharge under 40 CFR Part 439. The EPA has issued waste water Permit Number PAP120320 to the Lititz facility. The facility conducts monthly sampling and semiannual reporting to the Region III Office of the US Environmental Protection Agency.

The generation and disposal of wastes (hazardous and nonhazardous) are regulated by the Pennsylvania Department of Environmental Protection under Title 25 of the Pennsylvania Code, Article VII - Hazardous Waste Management, Article VIII - Municipal Waste, and Article IX - Residual Waste Management. The Lititz facility IPA Identification Number is Pad 003008942. All waste materials are disposed of in accordance with federal and state requirements. Wastes are disposed at approved disposal facilities. The preferred method for disposal of plant waste materials is incineration.

Solid Waste Incineration

Resource Conservation and Recovery Act (RCRA) hazardous wastes are disposed of by:

Laidlaw Environmental Services
3527 Whiskey Bottom Road
Laurel, MD 20724

Nonhazardous wastes are destroyed by either/or:

Lancaster County Solid Waste Management Authority Resource Recovery Facility
Marietta, Pennsylvania

Dutchess County Resource Recovery Agency
Poughkeepsie, New York

All disposal facilities and contractors employ high temperature (>1800°F) incineration.

Warner Lambert certifies that the Lititz facility is in substantial compliance with permit limits and environmental regulations. A letter of certification is provided in Appendix 7.

3.6.4.4.4. Goedecke AG Drug Product Facility

The environmental settings of the manufacturing and packaging facility is as follows:

The Warner-Lambert Goedecke AG facility is in Freiburg, Germany. Freiburg is located in extreme southwest Germany near the borders of Switzerland and France. Freiburg has a population of approximately 170,000 people, is a site of the regional government (Regierungs-Praesidium), and contains universities and industry.

The facility is located on approximately 6 acres of land in the northern section of the city of Freiburg. The site consists of approximately 15 buildings and employs an

average wc k force of about 1000 people. The major buildings are a chemical and pharmaceutical development facility including pilot plant, pharmaceutical manufacturing, chemical manufacturing, warehouses, Quality Assurance, powerhouse, and administration.

Air Resources

Air emissions are regulated in accordance with the German Federal Clean Air Act (Bundes-Immissions-Schutz-Gesetz). According to this law, pharmaceutical manufacturing operations require no air emission permits. However, for weighing, milling, blending, tablet compression, and tablet coating, high efficiency dust collection equipment are installed and used.

Water Resources

The Goedecke AG Freiburg facility receives its water from the Freiburg Energie und Wasserversorgungs AG (FEW). The FEW obtains its water from deep underground wells in the south of Freiburg. The water from the FEW enters the Goedecke AG site distribution system. Water used in the manufacture of pharmaceuticals is treated by reverse osmosis.

The waste water from general cleaning, housekeeping, and cleaning of manufacturing equipment is discharged by a gravity separator into the public sanitary sewer system. The waste water discharged is subject to waste water permit.

Waste water from cleaning and manufacturing operations which contain low levels of materials are collected by a separate sewage system. This waste water is handled by a separate gravity separator and sent to an underground storage system. The waste water is periodically discharged into tanker trucks and sent to a wet oxidation waste water treatment facility of a chemical plant, approximately 50 miles from Freiburg.

Land Resources

The property for the Goedecke AG Facility was purchased from the city of Freiburg in 1962 and was grassland until that time.

The area around the facility consists of industrial and urban land. The subsoil of the Goedecke facility consists of alluvial fans from the Dreisam River that has deposited a layer of unweathered gravel beds containing significant amounts of course clay approximately 35-meters deep. Intercalations of clay beds and weathered gravel have been found. The upper soil consists of landfill material that has been deposited during the development of the industrial site to a depth of 1 to 2 meters. The ground water lies approximately 16 to 20 feet below the surface. The site is on relatively flat land in the Rhein Valley with an elevation of approximately 740 feet above sea level.

Environmental Regulations

Air emissions are regulated by the Federal Clean Air Act (Bundes-Immissions-Schutz-Gesetz, (BImSchG)) and the Air Emissions Technical Guideline (Technische Anleitung Luft, [TA-Luft]). The State Industrial Control Authority (Staatliches Gewerbeaufsichtant) in the city of Freiburg regulates industrial air emissions.

In accordance with the BImSchG, no air permits are required for drug product manufacture. However, for erection and operation of facilities, a permit for construction of the facility is required in accordance with the State Building Regulations (Landesbauordnung [LBO]). Based on the evaluation and decisions of this authority, special limits, conditions, or monitoring requirements may be required.

For the Goedecke AG Freiburg facility, no special requirements are necessary. The applicable emission values of the TA-Luft are followed and the emissions are defined in Subchapter 3.1.3 (Total Dust). Monitoring requirements are not necessary.

Water discharge is regulated by the Environmental Protection Authority (Umweltschutzamt) of the City of Freiburg. The Water Permit Application is submitted to this Authority prior to the construction of the facility and installation of

equipment or prior to process changes which significantly affect the waste water discharged. The permit is issued as a Permit to Construct and Operate. The start of operations are provided to the authorities and inspection of operations is at the discretion of the Authorities.

The transportation and disposal of hazardous wastes are regulated by Federal and by the State Waste Act, the Federal Waste Control Regulation, and the State Waste Offering Duty Regulation. A disposal permit is issued by this local waste control authority.

The treatment, including pretreatment and storage of wastes, are regulated by the Federal Clean Air Act.

Goedecke AG certifies that the facility is in compliance with permit limits and environmental regulations of Germany. A letter of certification is provided in Appendix 8.

3.6.4.4.5. ISP Fine Chemicals Inc Facility

The ISP Fine Chemicals Inc plant is located in the city of Columbus, Ohio. The manufacturing area occupies approximately 10 acres of the more than 100 acre site. It is located approximately 0.8 miles north of I-70 and 1.4 miles west of I-270. The site consists of approximately 11 buildings and employs about 77 people The buildings are segregated according to particular purposes, ie, drum storing, maintenance and boilers, manufacturing, etc. The plant is located in the Walcutt Industrial Park, which is bordered by retail, commercial, residential, and industrial areas.

Air Resources

All reactor vessels, distillation units, solids processing equipment and associated point sources at the ISP facility are either permitted or on registration status with the Ohio Environmental Protection Agency (OEPA). Registration status means that the sources are considered very small and that no permit changes or notification are required to make process changes, as long as documentation is maintained to show that emissions

are below regulated levels. An analysis of the emissions from the [redacted] manufacturing process has determined that the air emissions are below the regulated levels and do not require any submissions to the OEPA. Multi-point air dispersion modeling of emissions from all ISP processes has been conducted according to the OEPA Air Toxics Emissions policy and shows all emissions to be below the level of concern at the nearest receptor.

Water Resources

The ISP facility receives all of its water from the Columbus Division of Water. The source of water is the Dublin Road Water Plant, which utilizes waste from 2 reservoirs on the Soloto River.

Noncontact cooling water and process wastewater are combined and flow through an on-site wastewater pretreatment plant. In the pretreatment plant, the wastewater passes through an automatic pH neutralization system and a settling tank. The treated wastewater is combined with sanitary wastes and discharged to the Columbus POTW system under pretreatment permit number JaOCISP5b0553. Wastewater from ISP is treated at the Jackson Pike Treatment Plant. Manufacture of [redacted] will not exceed permit limits.

Land Resources

The ISP facility is located on unconsolidated deposits of clay and silt, containing varying amounts of sand, gravel, and rock. The clay and silt are believed to be ground moraine (till) that were deposited by glaciers. The till overlies Devonian limestone at an estimated depth of 100 feet. The limestone may consist of either Delaware or Columbus formation. Silurian limestone underlies the Devonian formation.

Environment... Regulations

Air emissions from the ISP facility are regulated under Ohio Administrative Code (OAC) 3745-15, 3745-17, and 3745-21 for organic chemicals, particulate matter, and

photochemically reactive materials, respectively. Due to the batch nature of production, ISP is not a major source under Title V of the Clean Air Act Amendments. Air emission permits or registration status are assigned to each piece of manufacturing equipment. The reactors associated with the [redacted] manufacturing process are on registration status. Solids processing equipment used for the [redacted] manufacturing process are covered under Permit 01-4925. Calculations have been performed to document that emissions are below permitted levels.

Waste water discharges from the ISP facility are regulated under OAC 3745-3 and Columbus City Code Chapter 1145. ISP is currently under a Consent Compliance Order and Assessment of Administrative Fines with the City of Columbus regarding discharge of pollutants regulated under the Organic Chemicals, Plastics and Synthetic Fibers pretreatment subcategory (40 CRF 414). Compliance with this order will not be affected by production of [redacted].

Generation, accumulation, and disposal of hazardous waste is performed in accordance with OAC 3745-52, the Resource Conservation and Recovery Act, and the Hazardous Materials Transportation Act regulatory requirements.

ISP Fine Chemicals certifies that the Columbus facility is in compliance with permits, orders, and environmental regulations as described above. A letter of certification is provided in Appendix 6.

3.6.4.4.6. PACO Lakewood, New Jersey Packaging Facility

The PACO, New Jersey facility is located in the Lakewood Industrial Park, which is 5 miles southeast of Lakewood. The building at 1200 Paco Way is 150,000 sq ft. The Industrial Park is surrounded primarily by scrub pine trees and occasional deciduous trees. The terrain is coastal flatland with an elevation less than 50 feet above sea level. Two major bodies of water, the Metedeconk River and Barnegat Bay, are approximately 7 miles east of the facility.

The PACO Lakewood, New Jersey facility is in compliance with all permits and environmental regulations. A letter of certification is provided in Appendix 9.

3.6.4.5. Sites of Product Use

Atorvastatin 10-, 20-, and 40-mg tablets are intended for administration in hospitals, clinics, and under home care. Distribution will be nationwide, and the drug will be made available through physician offices and hospital and community pharmacies. With such usage, atorvastatin calcium and its metabolites would enter municipal sewage treatment systems throughout the United States.

3.6.4.6. Sites of Product Disposal

Returned and unused drug product will be returned via the Warner-Lambert Drug Distribution System. Material with inadequate shelf-life for distribution will be sent to the following facilities:

Warner-Lambert Company
400 W Lincoln Avenue
Lititz, PA 17543

or

The Ballentine Group
Munsonhurst Road
Franklin, NJ 07416

Returned products will be destroyed by high temperature (1800°F-2200°F) incineration in accordance with all applicable environmental regulations.

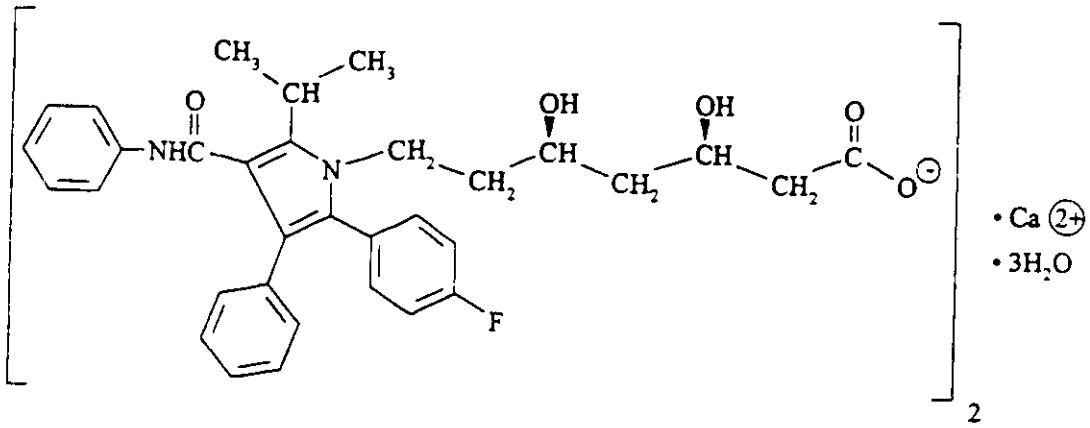
Material that does not meet specifications will be either reprocessed at the manufacturing sites specified and submitted as a supplement to the NDA or destroyed by high temperature (1800°F-2200°F) incineration in accordance with all applicable environmental regulations.

3.6.5. Identification of Chemical Substances that are the Subject of the Proposed Action

Atorvastatin calcium (USAN)

3.6.5.1. Nomenclature and Structure

3.6.5.1.1. Structure



3.6.5.1.2. Chemical Name

[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

3.6.5.1.3. Molecular Formula and Weight

$(C_{33}H_{34}FN_2O_5)_2Ca$	1158.38 (anhydrous calcium salt)
$(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$	1209.42 (calcium salt trihydrate)
$C_{33}H_{34}FN_2O_5$	557.65 (free acid)

3.6.5.1.4. Other Names

No other names are commonly used at this time.

3.6.5.1.5. CAS Registry Number

134523-03-8

3.6.5.1.6. Laboratory Code Numbers

CI-981 Calcium
PD 134298-38A

3.6.5.2. Physical and Chemical Properties

3.6.5.2.1. Appearance

A white to off-white powder

3.6.5.2.2. Thermal Behavior

The thermal behavior of crystalline atorvastatin calcium has been investigated using differential scanning calorimetry (DSC) and thermogravimetry (TGA). A representative combined DSC and TGA of a laboratory crystalline sample are shown in the Figure below. The DSC shows 4 distinct endothermic transitions at about 71°C, 109°C, 127°C, and 156°C. The 3 lower temperature transitions correspond to the weight loss transitions seen in the TGA. The total weight loss of 4.54% corresponds very closely with the theoretical water content of 4.47%. By mass spectrometry the weight loss was shown to be loss of water. The weight loss observed from 40°C to 80°C was 1.5% corresponding to the loss of 1 of the waters of hydration. The combined loss of 3% from 80°C to 132°C represents the loss from the crystal of the second and third waters of hydration. The DSC transition at 156°C corresponds to the melting of the crystal. The broad endotherm and weight loss starting at about 130°C is due to decomposition of the molecule.

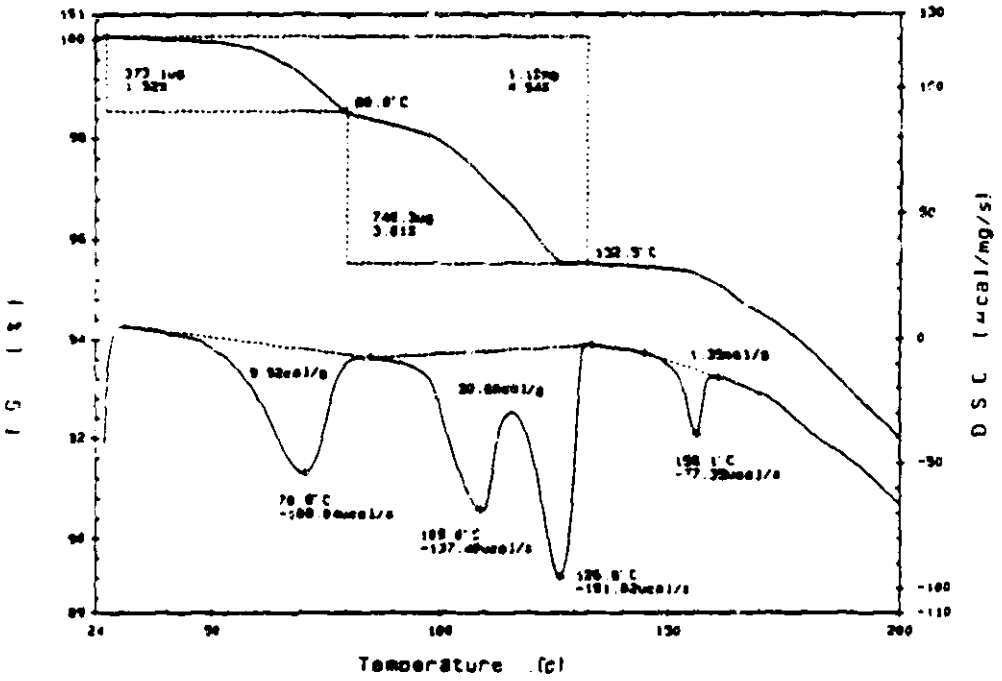


FIGURE 1 DCS and TGA Thermograms of Atorvastatin Calcium Form 1 Sample C-S-12, Files CS12C0-T and CS12C0-D

3.6.5.2.3. Dissociation Constants

The dissociation constant was determined using the amorphous form of the drug substance. The dissociation constant of the racemic compound was determined in methanol:water (1:1) by an ultraviolet spectroscopic method.

pK_a = 4.6.

The pK_a is consistent with the carboxylic acid function.

3.6.5.2.4. Ultraviolet Spectrum

The ultraviolet spectrum of atorvastatin calcium in 0.05 M phosphate buffer, pH 7.4 is shown in the figure below. An absorption maximum is found at 240 nm. The absorptivity at 240 nm is 37.9 mL (mg^{-1} cm^{-1}).

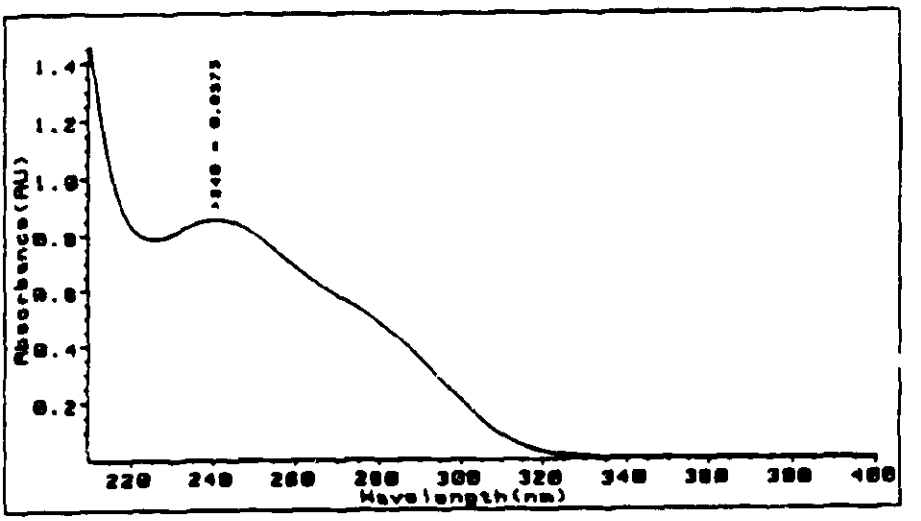


FIGURE 2 Ultraviolet-Visible Spectrum of Atorvastatin Calcium in 0.05 M pH 7.4 Phosphate Buffer, Lot XH4 0989, 0.033 mg/mL, RR 730-01588

3.6.5.2.5. Octanol-Water Partition Coefficient (expressed as Log P)

The partition coefficients of atorvastatin calcium were determined using octanol-water (shake-flask) using amorphous drug substance. The partition coefficients are provided in the table below.

Aqueous Phase	Log P
0.1 M HCl	3.66
0.05 M Acetate Buffer pH 4.0	3.18
0.05 M Phosphate Buffer pH 7.4	1.42

3.6.5.2.6. Solubility

The equilibrium solubility of atorvastatin calcium (Lot XH211194) was determined as a function of pH at 37°C. Approximately 100 mg of drug (equivalent to free-acid content) was placed with 10 mL of each respective solvent in ambered glass vials sealed with Teflon-lined screw caps, wrapped in Parafilm ¾ and rotated at 50 rpm in a rotating bottle apparatus at 37°C. Samples were taken at 5, 24, and 48 hours. The samples were centrifuged, and the supernatant solutions were filtered. The acidic samples were filtered using the 0.2 µm PVDF membrane with glass microfiber prefilter; the water and buffer samples were filtered using 0.45-µm glass microfiber filter. The filtrates were analyzed by HPLC. The equilibrium solubility results are summarized below.

Solvent Equilibrium Solubility (mg/mL)

Solvent	Equilibrium Solubility (mg/mL)
Water	0.11
0.1N HCl	0.01
0.05 M Sodium Phosphate Buffer (pH 7.4)	0.70

3.6.5.2.7. Vapor Pressure

Extensive vapor pressure studies have not been conducted on atorvastatin calcium Due to its melting range, the vapor pressure of the drug substance can be expected to be $<10^{-6}$ torrs.

3.6.5.3. Intermediates and Impurities

The isolated intermediates in the manufacture of atorvastatin calcium are [redacted], [redacted], and [redacted]. The [redacted] intermediate could appear in the final drug substance by incomplete saponification and removal in the final atorvastatin calcium manufacturing process. However, the reaction completion is monitored by in-process testing, and the observed range in batches is below the limit of quantitation [redacted].

The impurities present at levels >0.1% are:

- [redacted] has been observed in batches of drug substance at levels to [redacted]. It results from saponification of an [redacted] impurity, [redacted].
- [redacted] has been observed in batches of the drug substance at levels to [redacted]. It results from saponification of an [redacted] impurity, [redacted].
- [redacted] has been observed in batches of drug substance at levels to [redacted]. It results from saponification of an [redacted] impurity, [redacted].

Specifications for the above impurities of not more than 0.3% (w/w) have been proposed for the drug substance atorvastatin calcium.

3.6.5.4. Substances Used in Manufacturing of Drug Substance

The following substances are used in the manufacturing of the drug substance intermediate [redacted] at the Holland, Michigan, the Newport Synthesis LTD, and the ISP Fine Chemicals facilities noted in Section 3.6.4.3 of this environmental assessment

Starting Materials

The following, in part or in total, become a portion of [redacted]

[redacted]

Confidential Business Information (CBI)

Reagents, Solvents, and Auxiliary Materials

The following are used as processing aids (eg, catalysis, pH adjustment, solvents, etc) and do not become part of TBIN.

[redacted]

CBI

The following substances are used in the manufacturing of the drug substance intermediate [redacted] at the Holland, Michigan and Wacker-Chemie facilities noted in Section 3.6.4.3 of this environmental assessment.

Materials

The following, in part or in total, become a portion of [redacted]

[redacted] CBI

Reagents, Solvents, and Auxiliary Materials

The following are used as processing aids (eg, catalysis, solvents, etc) and do not become part of [redacted]

[redacted] CBI

The following substances are used in the manufacturing of atorvastatin calcium at the Holland, Michigan facility noted in Section 3.6.4.4.1 of this environmental assessment. The materials used are as follows:

- [redacted]

CBI

Reagents, Solvents, and Auxiliary Materials

The substances listed below are used in this process and do not become a part of the final chemical molecule:

- [redacted]

[redacted]

CBI

The following substances are used in the manufacturing of atorvastatin calcium at the Plaistow, Ireland facility noted in Section 3.6.4.4.2 of this environmental assessment The materials used are as follows:

[redacted][c]

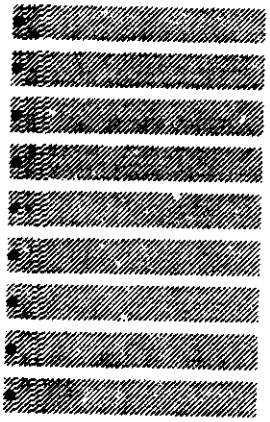
CBI

3.6.5.5. Substances Used in Manufacturing of Drug Product

The following substances are used in the manufacturing of atorvastatin tablets at the Lititz, Pennsylvania, and Freiburg, Germany facilities noted in Sections 3.6.4.4.3 and 3.6.4.4.4 of this environmental assessment, respectively:

[redacted]

[c] Intermediate from Holland, Michigan USA facility.



CBI

3.6.5.6. Metabolites from Administration of Drug Product

The mass balance and metabolic profile of atorvastatin calcium administration was determined in 6 healthy male volunteers who were given single daily 20-mg doses of unlabeled atorvastatin for 2 weeks followed by a single 20-mg (105.4 μCi) oral dose of [^{14}C]atorvastatin.

Six healthy volunteers were administered daily 20-mg doses of unlabeled atorvastatin tablets for 14 days followed by a single (2-×10-mg) capsule dose of [^{14}C]atorvastatin (105 μCi). Plasma, urine, and feces were collected serially for at least 336 hours following administration of the radiolabeled dose.

Urinary and fecal extracts were profiled by gradient HPLC with in-line radioactivity detection. Metabolite identification was accomplished by HPLC retention time, chromatographic comparison to reference standards, and by tandem mass spectrometry.

Mean (% RSD) cumulative urinary and fecal recovery of radioactivity was 1.23% (23%) and 89.4% (27%) of administered dose, respectively. Mean total recovery was 90.6% at the end of the 2-week collection period. Urine and fecal extracts contained 7 or more peaks.

Fecal excretion appears to be the primary route of atorvastatin elimination.

Not all fecal extracts at peak excretion intervals (24-96 hours postdose) produced profiles with distinct peaks since the radioactivity/gram of feces varied widely. The highest ^{14}C activity/gram feces of all fecal samples was from Subject 6 at the 24- to 48-hour interval. Comparisons of this chromatogram with a chromatogram of known standards demonstrated that 3 components made up 38.2% of the ^{14}C activity in the radiochromatogram, with the [redacted] contributing 11.7%, the [redacted] contributing 18.2%, and the [redacted] contributing 8.3% of the total radioactivity, respectively. Insufficient analytical method sensitivity prevented identification of smaller components in the HPLC fractions.

3.6.5.7. Degradation Products of Drug Substance

Stability studies early in the development of atorvastatin calcium drug substance showed the lability of the amorphous form to oxidation. The types of oxidative degradants identified are the types of oxidation products known to occur in compounds containing a similar pyrole moiety. An article describing the types of compounds identified and the potential mechanisms for their formation has been published in *Tetrahedron* and is provided in Appendix 3.

Evaluation of the effect of light on solutions of atorvastatin calcium was conducted using 100-µg/mL solutions prepared in acetonitrile:water (1:1). Solutions were placed into quartz flasks and exposed to UV light or fluorescent light. Control solutions were protected from light using foil-wrapped flasks. Atorvastatin calcium solutions exposed to UV or fluorescent light were unstable. After 6 hours under UV light or after 1 week under fluorescent light, essentially no drug remained. The results of this study are provided below.

Storage Time	Control (% Remaining)	Ambient (% Remaining)	Fluorescent (% Remaining)	UV Light (% Remaining)
6 Hours	--	--	99.0	0.00
24 Hours	--	96.7	91.3	0.00
48 Hours	--	97.9	82.4	--
72 Hours	--	100.1	68.7	--
1 Week	96.0	96.2	0.4	--
16 Days	94.7	94.7	--	--

The major nonoxidative degradant is identified as [redacted]. In dilute acid, the [redacted] and the [redacted] form an equilibrium mixture containing approximately 60% [redacted] and 40% [redacted]. The same ratio is reached whether the starting material is the [redacted] or the [redacted].

3.6.6. Introduction of Substances into the Environment

3.6.6.1. Substances Emitted from Drug Substance Manufacturing

3.6.6.1.1. Holland Chemical Facility

The materials used in the manufacturing and processing of [redacted], and atorvastatin calcium are listed in Section 3.6.5.4 of this environmental assessment. Further information on the processing and disposition of these materials is provided in this section.

Air

It was previously shown that the air emissions from the atorvastatin calcium manufacturing process consisted of minute quantities of [redacted] particulates and did not require a permit application for air emissions. The [redacted] emissions would fall to earth by rainout and be subject to the same mechanisms identified for product use.

Water

Water used in the atorvastatin calcium manufacturing process is sent to the chemical waste water treatment process and discharged to deepwell injection. Rinses from the cleaning of manufacturing equipment are sent to the chemical waste water treatment process and then sent to deepwell injection.

Solid

The solid waste from the atorvastatin calcium manufacturing process has been identified as [redacted], which is sent to spent catalyst storage for disposition.

Solvents

Organic solvents used in the atorvastatin process are recovered, sent to waste solvent collection tank, and disposed of by approved contractors.

Warner-Lambert certifies that the Holland Chemical facility is in compliance with permits and environmental regulations. A letter of certification is provided in Appendix 4.

3.6.6.1.2. Plaistow Ireland Chemical Facility

Plaistow Limited Manufacturing Chemists Inc certifies that the Plaistow Chemical Facility is in compliance with permit limits and environmental regulations in Ireland. A letter of certification is provided in Appendix 5.

3.6.6.1.3. Newport Synthesis LTD Facility

Newport Synthesis LTD certifies that their facility is in compliance with permit limits and environmental regulations of Ireland. A letter of certification is provided in Appendix 6.

3.6.6.1.4. Wacher-Chemie GmbH Facility

Wacher-Chemia certifies that their facility is in compliance with permit limits and environmental regulations of Germany. A letter of certification is provided in Appendix 6.

3.6.6.1.5. ISP Fine Chemicals Facility

ISP Fine Chemicals certifies that their facility is in compliance with permit limits and environmental regulations. A letter of certification is provided in Appendix 6.

3.6.6.2. Substances Expected to be Emitted From Drug Product Manufacturing

3.6.6.2.1. Lititz and Goedecke AG Drug Product Facilities

The Lititz, Pennsylvania and Freiburg, Germany formulation facilities utilizes atorvastatin calcium drug substance and excipients to produce the tablet dosage form. The list of excipients used for the tablet product is provided in Section 3.6.5.5. It is the practice of these facilities to account for 100% of the input ingredients in the final dosage form. This yield is calculated for each batch in accordance with GMPs. Any discrepancy of this expected yield is resolved prior to release of the batch for distribution.

The substances which may be expected to be emitted into the environment are very small quantities of product dust. This product dust would be assumed to be in the same ratio as its composition in the product formulation.

Product Dust Control

During the various steps of formulation of the drug product dosage form, dust is collected through a series of local vacuum system pickups. These sources are connected to collection filters where 95% of the product dust is collected for disposal. Particulate emissions after control are regulated by the air emission permit.

Dust so collected is periodically removed from the unit and destroyed offsite by high temperature (1800°F-2200°F) incineration as a nonregulated pharmaceutical waste. In general, all product residuals are collected in a dry state and are not entering waste water treatment systems. Prior to any washings, systems and equipment are thoroughly vacuumed to remove dust, and only negligible amounts are discharged to sewers.

Warner-Lambert certifies that the Lititz and Freiburg facilities are in compliance with permits and local environmental regulations. Letters of certification are provided in Appendices 7 and 8, respectively.

3.6.6.2.2. PACO Lakewood, New Jersey Facility

No substances are expected to be emitted from drug product packaging.

PACO Lakewood, New Jersey certifies that their facility is in compliance with permit limits and environmental regulations. A letter of certification is provided in Appendix 9.

3.6.6.3. Substances Expected to be Emitted Into Environment From Product Use

The substances which may be expected to be emitted into the environment from use of this product are atorvastatin acid and its metabolites. The metabolites from the other excipients are common materials used in medications throughout the United States, and the incremental usage increase from this product is minimal.

The principal route of atorvastatin entering the environment in any manner is its use and elimination by human patients. The maximum expected emitted concentration (MEEC) value for atorvastatin calcium is based on the assumption that none of the drug is metabolized and is provided in the following equation. This equation is based on the assumption that [redacted] of atorvastatin calcium would be manufactured annually as provided in the 5-year production estimate.

Production of [redacted]/year of atorvastatin calcium production results in an EIC value of [redacted].

The source of this equation is:[1]

$$EIC\ (ppm) = A \times B \times C \times D$$

Where: A = Kgs/year production
B = l/liters per day entering POTWs[a]
C = Year/365 days
D = 10^6 mg/kg (conversion factor)

---

[a] 1.115×10^{11} liters/day entering publicly owned treatment works.

However, it was shown in Section 3.6.5.6 that 3 components made up 38.2% of the ^{14}C activity in the radiochromatograms in studies of atorvastatin calcium metabolism, with the [redacted] metabolite contributing 11.7%, the [redacted] metabolite contributing 18.2%, and the [redacted] contributing 8.3% of the total radioactivity, respectively. Atorvastatin calcium is extensively metabolized.

3.6.6.4. Substances Expected to be Emitted Into Environment From Product Disposal

Drug substance and tablets that fail specifications, pass expiration period, or are returned from the field are destroyed by high temperature (1800°F-2200°F) incineration by approved and regulated facilities.

Note: Sections 3.6.7 through 3.6.11 have been intentionally omitted.

---

[1] Guidance for industry for the submission of an environmental assessment in human drug applications and supplements. CDER Nov, 1995

3.6.12. List of Preparers

Sean T. Brennan, PhD
Worldwide Regulatory Affairs

Alexander J. Brankiewicz, BSChE
Worldwide Regulatory Affairs

IND 35,544

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Byron Scott, R.Ph.
Director, FDA Liaison
Worldwide Regulatory Affairs
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, Michigan 48106-1047

JUN 13 1996

Dear Mr. Scott:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets.

We also refer to your submission dated February 22, 1996, serial number 249, which requested our comment on your proposed trade name "Lipitor™" for this product. Additionally, we refer to your submission dated April 17, 1996, serial number 259, which requested our comment on your proposed trade name "Thor™" for this product.

The Agency finds "Lipitor™" to be acceptable as a trade name for this product. However, the Agency finds "Thor™" not to be acceptable as a trade name because of two other existing proprietary names that potentially look like or sound like "Thor".

If you have any further questions, please contact Ms. Julie Rhee, Consumer Safety Officer, at (301) 443-3510.

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolism
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

3.6.13. Certification

The undersigned officials certify to the best of their knowledge that the information presented is true, accurate, and complete for preparation of the environmental assessment.

Sean T. Brennan, PhD for
Senior Director
Worldwide Regulatory Affairs
Parke-Davis Pharmaceutical Research

10/25/96
Date

Alexander J. Brankiewicz, BSChE
Manager
Worldwide Regulatory Affairs
Parke-Davis Pharmaceutical Research

10/25/96
Date

3.6.14. List of References

1. Guidance for industry for the submission of an environmental assessment in human drug applications and supplements. CDER Nov, 1995.

2. Food and Drug Administration. Environmental assessment technical assistance handbook. 1987, NTIS, Washington, DC.

3.6.15. List of Appendices

Tab

APPENDIX 1

INDICATIONS AND USAGE SECTION FOR PROPOSED PACKAGE INSERT

Text	Source Material	Volume Page
Homozygous Familial Hypercholesterolemia		
In an uncontrolled study, 41 patients ages 6 to 51 years with homozygous FH or with severe hypercholesterolemia who had ≤15% response to maximum combination drug therapy received daily doses of 40 to 80 mg of TRADENAME. Thirty-five patients had a reduction in LDL-C ranging from 11% to 55%. In 2 patients with absent receptor function, mean LDL-C reduction was 19%. Six patients had less than a 10% response to treatment.	981-54, RR 720-03702 981-80, RR 720-03637	
INDICATIONS AND USAGE		
Therapy with lipid-altering agents should be a component of multiple risk factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other nonpharmacological measures has been inadequate (see *NCEP Treatment Guidelines*, summarized in Table 5).	"Class" Labeling	

ATORVASTATIN

(Atorvastatin Calcium Tablets)
ANNOTATED PACKAGE INSERT

Text	Source Material	Volume Page
TRADENAME 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.	Integrated Summary of Efficacy	
TRADENAME is indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia.	981-54, RR 720-03702 981-80, RR 720-03637	

APPENDIX 2

ATORVASTATIN CALCIUM MATERIAL SAFETY DATA SHEET

WARNER LAMBERT

Material Safety Data Sheet

Printed Date : 3/27/96

Section 1 Chemical Product and Company Identification

Product Name :	[R-(R*,R*)]2-(4-Fluorophenyl)-beta,delta-Dihydroxy-5-(1-Methylethyl)-3-acid, Hemicalcium salt
MSDS # :	288.00
Issue Date :	10-MAY-93
Supersede :	23-SEP-91
Revision :	1
Warner-Lambert ID Number :	134298-0038A
Process Number :	CI-981
Manufacturing Division :	

Parke-Davis
2800 Plymouth Road
Ann Arbor
MI
48105
Company Contact
G Kreick
(313)996-7000

Section 2 Composition/Information on Ingredients

Ingredient Name :	[R*-(R*, R*)]2-(4-Fluorophenyl)-a-?-Dihydroxy-5-(1-Methylethyl)-3-Phenyl-4-[(Phenylamino)Carbonyl]-
Concentration Percent :	100
CAS Number :	ND
OSHA PEL :	ND
ACGIH TLV :	ND

Section 3 Hazards Identification

Potential Health Effects

Therapeutic Class Lipid modifier; Reductase Inhibitor

Section 4 First Aid Measures

Eyes :	Flush with water for 15 minutes.
Skin :	Wash with soap and water until free of residue.
Ingestion :	Seek medical attention.
Inhalation :	Remove from exposure. Seek medical attention.

Section 5 Fire Fighting Measures

Flash Point (Method) :	NA
Autoingnition Temperature :	ND
LEL(%) :	NA

Section 5	Fire Fighting Measures	Contd

UEL(%) :	NA
Fire and Explosion Hazards :	Unusual Fire Hazards: ND; Unusual Explosion Hazards: ND
Extinguishing Media :	CO2, Dry Chem, Foam, Water Spray
Fire Fighting Instructions :	Use approved self-contained breathing apparatus.
Hazardous Combustion Products :	Oxides of Carbon and Nitrogen, Hydrogen Fluoride

Section 6 Accidental Release Measures

Wear self-contained breathing apparatus and appropriate protective clothing. Collect and place in a suitable container for future disposal.

Section 7 Handling and Storage Precautions

Store in a cool, dry location, isolated from oxidizing agents. If unusual exposures are expected, an Industrial Hygiene review of work practices and controls is recommended.
The above personal protective equipment represents the minimum protection recommended. Use handling method to minimize dust generation. Avoid skin contact or inhalation of dusts. Wash face, hands and forearms on leaving work area.

Section 8 Exposure Controls/Personal Protective Equipment

Engineering Controls :	General ventilation; local exhaust ventilation.
Personal Protective Equipment	
Eye/Face Protection :	Safety Glasses
Skin Protection :	Coveralls and gloves
Respiratory Protection :	1/2-face piece negative pressure respirator with approved dust filter.

Section 9 Physical and Chemical Properties

Molecular Formula :	C33H34N2FO5.1/2Ca
Molecular Weight :	578
Appearance :	White to off-white
Odor Threshold :	ND
Melting Point :	163-180
Boiling Point :	NA
Specific Gravity (Water = 1) :	ND
Percent Volatile by Volume :	NA
Vapor Pressure :	ND
Vapor Density :	ND
Evaporation Rate :	ND
Solubility (Water) :	No
Solubility (Other) :	MeOH, Acetone, THF/water, acids
Miscellaneous Information :	Physical State: Solid

Section 10 Stability and Reactivity

Chemical Stability :	Stable
Conditions to Avoid :	NA
Incompatible Materials :	ND
Hazardous Polymerization :	NO
Miscellaneous Information :	Conditions to Avoid:NA;

Section	10	Stability and Reactivity	Contd.

Section	11	Toxicological Information

Ingredient Name : [R*-(R*, R*)]2-(4-Fluorophenyl)-a-?-Dihydroxy-5-(1-Methylethyl)-3-Phenyl-4-[(Phenylamino)Carbonyl]-

Miscellaneous Information : Toxicity Information: Rat Oral LD50: >5000 mg/kg; Mouse Oral LD50: >5000 mg/kg; Rabbit Dermal LD50: >2000 mg/kg; Not an irritant in animal eye and skin tests. Not a sensitizer in the modified Beuhler test. Not mutagenic in Ames bacterial assay. Some weight loss effects on the liver have been seen in 13-week studies in dogs and rats.; Effects of Occupational Overexposure: ND;

Section	12	Ecological Information

ND

Section	13	Disposal Information

Dispose of in accordance with local, state and federal regulations or the authority having jurisdiction. Incineration in a permitted incinerator is the preferred disposal method.

Section	14	Transportation Information

DOT Shipping Name : ND
DOT Hazard Class : ND
DOT Shipping Label(s) : ND
Shipping Limitations ND
Miscellaneous Information : NA Number: NA ;Storage Area Temperature Requirements: No RestrictionsND

Section	15	Regulatory Information

U.S. Federal Regulations : NA

Section	16	Other Information

OSHA Hazard Communication Labels : ND

Disclaimer : The information contained within this data sheet is based on currently available scientific studies and is accurate and reliable to the best of our knowledge. Warner-Lambert makes no other warranties, expressed or implied, and assumes no responsibility or liability for injury or damage caused by the material if it is misused or reasonable safety procedures are not followed as specified in this data sheet.

APPENDIX 3

REFERENCE PUBLICATION

Tetrahedron Vol. 49, No. 10, pp. 1979-1984, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Photodecomposition of CI-981, an HMG-CoA Reductase Inhibitor

Timothy R. Emrley*†, Charles E. Coleman†, Scott A. Clippert,
Susan E. Uhlendorf‡ and Michael D. Reily‡

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Warner-Lambert Company, 2800 Plymouth Road,
Ann Arbor, MI 48106, USA

(*Received in USA* 23 *November* 1992)

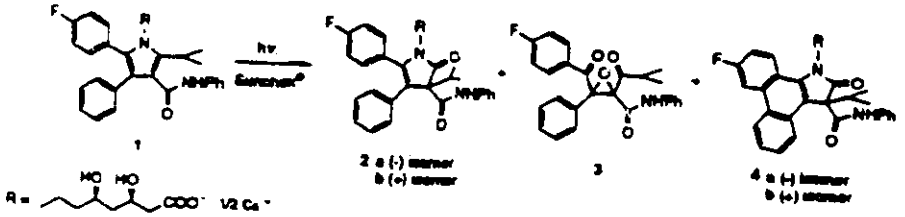
† Department of Chemical Development
‡ Department of Chemistry: Spectroscopy

Key Words: Photooxidation; pyrrole; lactam; phenanthrene; epoxidation

Abstract: Upon exposure to intense simulated sunlight, CI-981 (1) readily decomposes into three major by-products. This paper reports on the products formed when 1 is decomposed in acetonitrile/water solutions under intense simulated sunlight, ultraviolet light filtered at 254 nm and visible light. Included is a discussion of the isolation of the major by-products and possible mechanisms for the photooxidative processes which lead to them.

INTRODUCTION

Previous articles from our laboratories have documented that CI-981 [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (1) functions as an efficient inhibitor of HMG-CoA reductase.[1] Upon exposure to intense simulated sunlight, the compound in solution readily decomposes into three major by-products (Scheme 1).



Scheme 1. Photodecomposition of 1 Under Intense Simulated Sunlight

This report discusses the possible mechanisms for the formation of the photodegradation products of 1. The lactam products (-)-5-(4-fluorophenyl)-2,3-dihydro-β,δ-dihydroxy-3-(1-methylethyl)-2-oxo-4-phenyl-3-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (2a) and (+)-5-(4-fluorophenyl)-2,3-dihydro-β,δ-dihydroxy-3-(1-methylethyl)-2-oxo-4-phenyl-3-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (2b) and the diketoepoxide product 3-:(4-fluorophenyl)carbonyl:-2-(2-methyl-1-oxopropyl)-N,3-diphenyl-2-oxiranecarboxamide (3) require visible light, a sensitizer and triplet oxygen. The photodecomposition of pyrroles to 2,5-diketo-3,4-epoxy products has been reported.[2-5] Previous articles have reported lactam formation from pyrrole photooxidation.[6-8] Migration of the 5 substituent to the 4 position, as demonstrated in the rearrangement of the isopropyl group in lactams 2 (a and b), has also been reported.[2,4,5,9,10] The formation of the phenanthrene products (-)-9-fluoro-2,3-dihydro-β,δ-dihydroxy-3-(1-methylethyl)-2-oxo-3[(phenylamino)carbonyl]-1H-dibenz[e,g]indole-1-heptanoic acid hemicalcium salt (4a) and (+)-9-fluoro-2,3-dihydro-β,δ-dihydroxy-3-(1-methylethyl)-2-oxo-3[(phenylamino)carbonyl]-1H-dibenz[e,g]indole-1-heptanoic acid hemicalcium salt (4b) requires the irradiation of 2 (a and b) with light from the ultraviolet region. Phenanthrene formation from the photocyclization of stilbenes has been reported.[10-14]

EXPERIMENTAL SECTION

Photodecomposition of 1: One hundred milliliters of a 0.50 mg/mL solution of 1 in 60/40 acetonitrile/water was irradiated in an open beaker in an Atlas Suncheck® exposure instrument (Xenon arc lamp, set to 0.35 W/m^2 at 340 nm) at a distance of 100 mm from the lamp source. The solution was assayed by HPLC at 15-minute intervals. Figure 1 shows an HPLC chromatogram of the solution after 60 minutes. After 90 minutes, the peak corresponding to the starting material had completely disappeared.

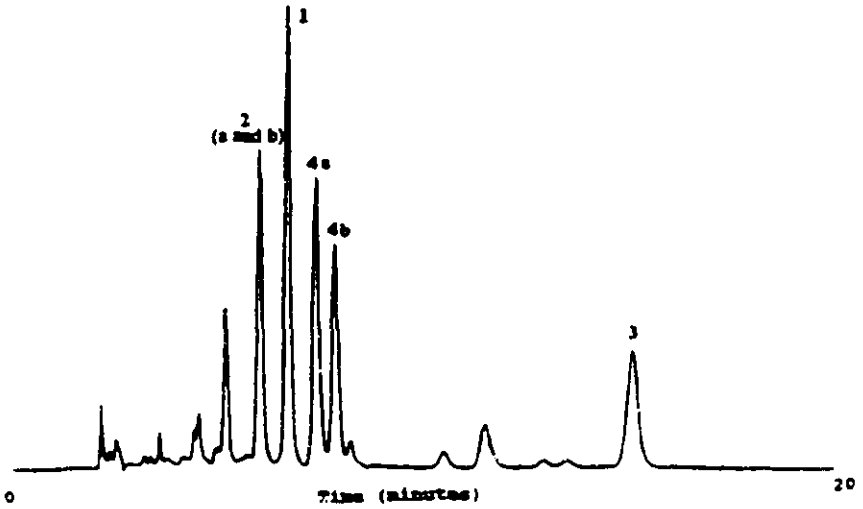


FIGURE 1. HPLC chromatogram of a 0.50 mg/mL solution of 1 in 60/40 acetonitrile/water after 60 minutes of exposure to intense simulated sunlight. Analytical HPLC conditions are described in the Experimental Section.

The analytical HPLC system used to monitor photodecomposition reactions included an Alltech Econosphere® 5 µ C18 column (150 mm x 4.6 mm I.D.), 57:23:20 0.05 M citric acid (pH 4.0 with NH_4OH):CH_3CN:THF, 2.0 mL/minute, 254 nm detection.

Wavelength-specific photodecomposition experiments were also carried out on similar solutions of 1 in 60/40 acetonitrile/water. The solutions were irradiated in an open beaker for 3 hours at a distance of 100 mm from the following lamp sources: 254 nm (Spectroline® Model CX-20), 365 nm (Spectroline® Model CX-20), and visible (100 W, 120 V, tungsten spotlight). The same experiments were repeated with 0.50 µg/mL methylene blue added as a sensitizer. Table 1 summarizes the formation of the major by-products expressed as a normalized percentage of the total HPLC area of known products under the reaction conditions described above.

TABLE 1. Formation of By-Products of 1

hν Source	Sensitizer	% Area Normalization (HPLC)			
		1	2 (a + b)	3	4 (a + b)
Suncher®	-	0	44	8	48
254 nm	-	79	7	1	14
254 nm	Methylene Blue	79	8	1	12
365 nm	-	0	20	16	64
365 nm	Methylene Blue	0	21	15	64
Visible (W)	-	100	0	0	0
Visible (W)	Methylene Blue	0	69	31	0

Preparative Chromatography: Isolation of the individual by-products outlined in Scheme 1 required both reverse-phase and normal-phase preparative chromatography. The conditions for reverse-phase chromatography were:

Column: Rainin Dynamax® 8 µ C18, 300 mm x 41.4 mm I.D.
Mobile Phase: 50:30:20 0.05 M citric acid (pH 4.0 with NH_4OH):CH_3CN:THF
Flow Rate: 25 mL/minute

The conditions for normal-phase chromatography were:

Column: Rainin Dynamax 8 µ silica gel, 300 mm x 41.4 mm I.D.
Mobile Phase: 60:36:4 hexane:$CHCl_3$:MeOH
Flow Rate: 25 mL/minute

The preparative chromatographic fractions were combined based on their purity by HPLC. Rotational data conducted on isolated compounds 2 (a,b) and 4 (a,b) was used to designate each isomer as (+) or (-).

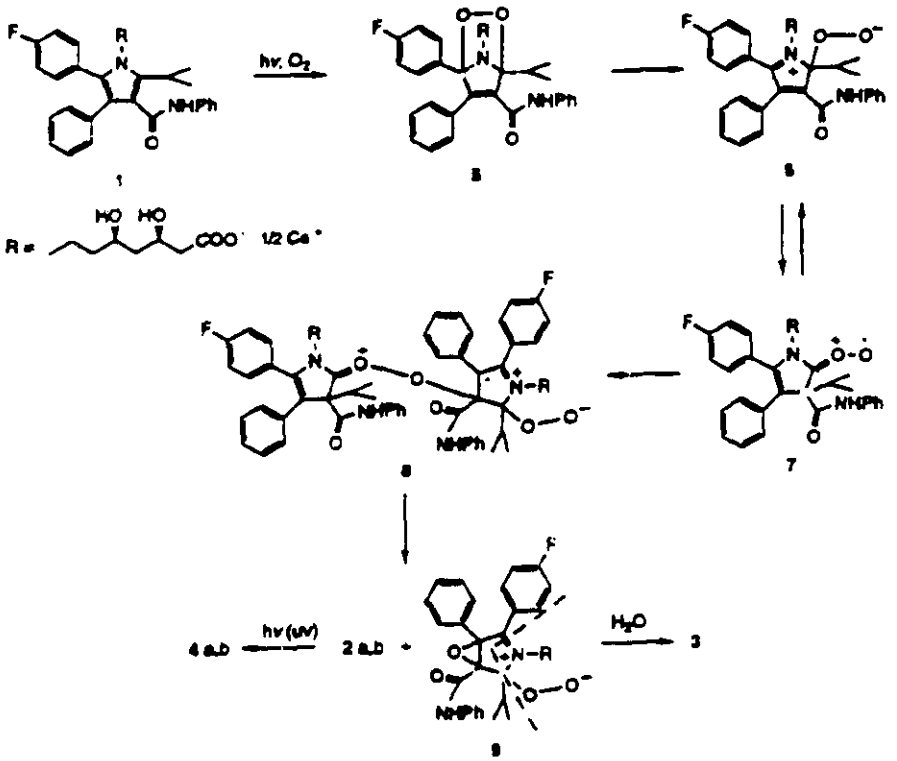
Isolation of 3: Ten grams of 1 was dissolved in 4.5 L of 70/30 acetonitrile/water and irradiated in open beakers for 25 hours under intense simulated sunlight in an Atlas Suncheck® exposure instrument. The acetonitrile was evaporated off in vacuo forming 8.8 g of a water insoluble oil. This oil was dissolved in 25 mL of acetonitrile and sonicated for 10 minutes. The crude 3 which precipitated out of solution was recrystallized from 3 mL of 2/1 hexane/chloroform. Crystalline 3 (100 mg) was recovered. The FAB mass spectrum of 3 has a molecular ion peak at m/z 432 (M+1). Signals at 189.9 ppm and 206.6 ppm in the ^{13}C-NMR of 3 in $CDCl_3$ correspond to the two ketone carbons. Chemical shifts at 74.2 and 70.8 ppm are assigned to the quaternary carbons bearing the epoxide oxygen.

Isolation of 2a and 2b: The mother liquor from the first precipitation of 3 described above was preparatively chromatographed under reverse-phase conditions. The fraction corresponding to purified 2 (a plus b) was concentrated to aqueous and extracted with chloroform. Separation of the individual (-) and (+) isomers (2a and 2b, respectively) required lactonization of the mixture with HCl at 60°C, normal-phase chromatography to separate the resulting lactones and base hydrolysis of the individual isomers at 65°C with 1.0 M sodium hydroxide. The FAB mass spectrum of 2a (Na^+ salt) has molecular ions at m/z 597 (M+1) and at m/z 619 $(M+Na)^+$. The FAB mass spectrum of 2b is identical to that of 2a. A signal at 177.2 ppm in the ^{13}C-NMR spectrum of 2a in d-DMSO corresponds to the newly-formed lactam carbonyl. In a two-dimensional ^{13}C-^{13}C INADEQUATE[15] experiment, a quaternary carbon signal at 68.5 ppm demonstrates connectivity to the lactam carbonyl, the benzamide carbonyl, the methine carbon in the isopropyl moiety and an unsaturated alicyclic carbon bearing a phenyl group.

Isolation of 4a and 4b: The reverse-phase column described in the isolation of 2a and 2b also separated the individual (-) and (+) isomers 4a and 4b. Each isomer was lactonized with HCl at 60°C and further purified by preparative normal phase chromatography. Base hydrolysis of the individual isomers with 1.0 M sodium hydroxide at 65°C formed the sodium salts of 4a and 4b. The FAB mass spectra of both 4a and 4b (Na^+ salts) have molecular ion peaks at m/z 595 (M+1) and m/z 617 $(M+Na)^+$. ^{1}H and ^{13}C-NMR spectra are consistent with the assigned phenanthrene structure.

RESULTS AND DISCUSSION

In 1960, Wasserman and Liberles reported a 4,4-disubstituted lactam product from the irradiation of 2,3,4,5-tetraphenylpyrrole with a 150-watt flood light in the presence of methylene blue.[2] The same article reports the formation of a tetraphenyl diketoepoxy photooxidation product of the starting pyrrole. Rio, et al.[16] have suggested that these products arise through a hydroperoxide intermediate, which in turn is derived from an endoperoxide formed at the 2,5 position in the pyrrole ring. Scheme 2 shows a possible mechanism in the oxidative rearrangements leading to 2 (a,b) and 3. Intermediate 5, an endoperoxide formed at the 2,5 position in 1, further reacts to the peroxy bridged dimer 8, which is derived from 6 and 7 in equilibrium. From 5, 2 (a,b) and 9 are formed, and 9 continues on to the diketoepoxide 3 in the presence of H_2O. Photocyclization of 2a and 2b in the presence of ultraviolet radiation produces 4a and 4b, respectively.



Scheme 2. Photodecomposition of 1

Upon exposure to ultraviolet light for 3 hours at 254 nm, 1 is photodegraded to lactams 2a and 2b and further to phenanthrenes 4a and 4b at a relatively slow rate when compared to exposure to 365 nm (Table 1). The reaction rate is not affected by the presence of methylene blue at 254 nm. Complete photodecomposition of 1 to by-products 2 (a, b), 3, and 4 (a, b) occurs rapidly at 365 nm regardless of the presence of methylene blue. Only under visible light are the energy transfer properties of methylene blue required for the rapid photooxidation of 1. The starting material is completely converted under the visible tungsten spotlight in the presence of methylene blue; in stark contrast, no reaction occurs under visible light in the absence of photosensitizer. The photodecomposition of 1 under simulated sunlight proceeds rapidly in solution without a sensitizer added. There is, however, increasing amounts of phenanthrenes 4 (a and b) generated from 2 (a and b). These products are capable of acting as sensitizers allowing energy transfer in order to form triplet oxygen at lower wavelengths (e.g., 254 and 365 nm). The "low visible" wavelengths in the 365 nm range of the broad-spectrum simulated sunlight are most responsible for the rapid photooxidation which converts 1 to 2a and 2b.

The analysis of the stability of pharmaceuticals such as **1** require simulated sunlight sources which, unlike most flood lamps, do not filter out ultraviolet light. In the photodecomposition of **1** in solution, the presence of oxygen, low wavelength visible light and phenanthrenes **4a** and **4b** acting as sensitizers are necessary for the formation of lactams **2a** and **2b**. Also, the formation of lactams **2** (a and b) and the presence of ultraviolet light are necessary preconditions for the photocyclization reaction leading to **4** (a and b). The apparent interdependence of **2** and **4** in the accelerated photodecomposition of **1** suggests that the presence of a trace amount of either product in the starting solution is necessary for the process to begin.

ACKNOWLEDGEMENTS

We would like to thank Drs. Donald Butler and Tom Nanninga for cooperation in providing bulk materials. We thank the editors for useful insights into photodegradative mechanisms.

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APPENDIX 4

WARNER-LAMBERT CERTIFICATION OF HOLLAND CHEMICAL FACILITY

59

Warner-Lambert Company
182 Tabor Road
Morris Plains, New Jersey 07950
201 540-4355
Fax: 201 540-5316

James C. Lime
Vice President
Environmental Affairs & Compliance

WARNER LAMBERT

October 22, 1996

Mr. A. Brankiewicz
Warner-Lambert
2800 Plymouth Road
Ann Arbor, MI 48105

Re: **Environmental Certification of Holland, MI Facility - Atorvastatin NDA Submittal**

Dear Mr. Brankiewicz:

This memorandum certifies that our Holland facility is in compliance with all local and national environmental laws and regulations.

The facility is also in compliance with all emission requirements set forth in all permits.

The increase in production at the Holland, MI facility due to the manufacture of Atorvastatin Drug Substance and its intermediates at the Holland, MI facility is not expected to affect compliance with current emission requirements of compliance with environmental laws.

Sincerely,

James C. Lime

APPENDIX 5

CERTIFICATION OF PLAISTOW CHEMICAL FACILITY

61

PLAISTOW
MANUFACTURING CHEMISTS :D

LITTLE ISLAND, CORK, IRELAND

13 March 1996

CERTIFICATION OF PLAISTOW'S FACILITY

The Plaistow facility is in compliance with all local and national environmental laws and regulations.

The Plaistow facility is in compliance with all emission requirements set forth in all permits.

The increase in production at the Plaistow facility due to manufacture of Atorvastatin at the Plaistow facility is not expected to affect compliance with current emission requirements or compliance with environmental laws

Signed

Sean O'Keeffe
Managing Director

V.A.T. No 9[illegible]
Registered Office Little Island Cork Incorporated in Ireland No 58[illegible]
Directors
Sean P. O'Keeffe (Managing) Francis D. Daly

APPENDIX 6

CERTIFICATIONS OF DRUG SUBSTANCE INTERMEDIATE MANUFACTURING SITES

FINE CHEMICALS Inc.

1979 Atlas Street • Columbus, OH 43228 • Tel: 614-876-3637 • Fax: 614-876-9532

October 22, 1996

Dr. Philip Simonson
Manager, Chemistry, Manufacturing, and Controls
World-Wide Regulatory Affairs
Pharmaceutical Research Division
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

Dear Dr. Simonson:

The following certification is being made in support of the NDA being filed for the manufacturing of the atorvastatin calcium intermediate, TBIN, at the ISP Fine Chemicals Inc. facility located at 1979 Atlas Street, Columbus, Ohio.

The ISP Fine Chemicals Inc. facility is in compliance with all local and national environmental laws and regulations.

The ISP Fine Chemicals Inc. facility is in compliance with or on an enforceable schedule to be in compliance with all emission requirements set forth in all permits.

The increase in production at the ISP Fine Chemicals Inc. facility due to manufacture of TBIN at the ISP Fine Chemicals Inc. facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Sincerely,

Paul Taylor

Paul D. Taylor, PhD
Vice President and General Manager

Newport

Newport Synthesis Limited,
Baldoyle Industrial Estate, Dublin 13, Ireland.
Tel: + 353 1 832 0020. Fax: +353 1 832 0026. Telex: 30189.

22 October 1996

Dr. Jim Zeller
Chemical Development Division
Parke-Davis
188 Howard Avenue
Holland
MI 49424

Certification of Newport Synthesis' Facility

Dear Dr. Zeller,

With reference to your enquiry I am pleased to confirm that The Newport Synthesis Ltd facility is in compliance with all local and national environmental laws and regulations.

The Newport Synthesis Ltd facility is in compliance with all emission requirements set forth in all permits.

The increase in production at the Newport facility due to the manufacture of TKIN is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Yours sincerely,

James O'Daly
Managing Director

WACKER
Wacker-Chemie GmbH

An/To Dr. Jim Zeller
Firma/Company PARKE-DAVIS
Fax-Nr. 001616-392-8916
Von/From Dr. Deinhammer Wolfgang
Abt./Dept. L-S-P/WR
Pers. Tel.- Nr. 08677-833673
Pers. Fax-Nr. 08677-833318

Telefax

Seiten/Pages 1
Datum/Date 10.23.96

Certification of Wacker's Facility

The Wacker facility is in compliance with all local and national environmental laws and regulations.

The Wacker facility is in compliance with all emission requirements set forth in all permits.

The increase in production at the Wacker facility due to the manufacture of diketone is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Signed: W. Deinhammer

(Dr. Deinhammer, Head of Production, R + D Organics)

Sitz München Amtsgericht München HRB 3468
Geschäftsführer: Kurt C. Engels (Sprecher), Klaus von Lindeiner, Rudolf Staudigl, Peter-Alexander Wacker
Vorsitzender des Aufsichtsrates: Jürgen Hermann

Wacker Chemie GmbH
Johannes-Hess-Str. 24
D-84489 Burghausen
Telefon 08677 - 83-0
Telefax 08677 - 83-

FORM13.SAM

GESAMT SEITEN 8

APPENDIX 7

WARNER-LAMBERT CERTIFICATION OF LITITZ
PHARMACEUTICAL FACILITY

Warner-Lambert Company
182 Tabor Road
Morris Plains, New Jersey 07950
201 540-4355
Fax 201 540-5316

James C. Lime
Vice President
Environmental Affairs & Compliance

67

WARNER LAMBERT

March 27, 1996

A. Brankiewicz
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

Re: **Environmental Certification of Lititz, PA Facility - Atorvastatin Tablet NDA Submittal**

Dear Mr. Brankiewicz:

The Lititz, PA facility is in compliance with all local and national environmental laws and regulations. The Lititz, PA facility is also in compliance with all emission requirements set forth in all permits.

The increase in production at the Lititz, PA facility due to the manufacture of Atorvastatin Tablets at the Lititz, PA facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Sincerely,

James C. Lime

APPENDIX 8

WARNER-LAMBERT CERTIFICATION OF FREIBURG PHARMACEUTICAL FACILITY

GODECKE AKTIENGESELLSCHAFT BERLIN

Werk Freiburg
March 19, 1996

PARKE-DAVIS PHARMACEUTICAL
RESEARCH DIVISION
Warner Lambert Company
Attn. Mr. A. Brankiewicz
Worldwide Regulatory Affairs
2800 Plymouth Road
Ann Arbor, Michigan 48105
USA

Freiburg Environmental Assessment Information for Atorvastatin NDA

Dear Mr. Brankiewicz,

the Goedecke facility located at Freiburg, Germany is in compliance with all local and national environmental laws and regulations.

Further, the Goedecke facility is in compliance with all emission requirements set forth in the relevant licenses with the exception of two: the pH-value and documentation of waste water discharged. Nevertheless, with regard to these requirements, Goedecke is on an enforceable schedule to be in compliance.

The increase in production at the Goedecke facility due to manufacture of Atorvastatin at the Goedecke facility is not expected to affect compliance with current emission requirements or compliance with environmental laws and regulations.

Sincerely

GOEDECKE AG

Plant Manager

Dr. J. Werani

Safety and Environmental Affairs

A.Rapp

APPENDIX 9

CERTIFICATION OF PACO LAKEWOOD, NEW JERSEY
PACKAGING FACILITY

71

PACO
PHARMACEUTICAL SERVICES, Inc.
1200 Paco Way • Lakewood, NJ 08701
TEL 908-367-9000 • FAX 908-364-5266

October 22, 1996

Parke Davis Pharmaceutical
Attn: Philip Simonson, Ph. D.
Worldwide Regulatory Affairs
2800 Plymouth Road
Ann Arbor, MI 48105

Re: Certification of Lakewood, New Jersey Facility - Atorvastatin Tablets NDA Submittal

Dear Dr. Simonson:

The PACO facility at Lakewood, New Jersey is in compliance with all local and national environmental laws and regulations.

The PACO facility at Lakewood, New Jersey is also in compliance with all emission requirements set forth in all permits

The increase in production at the PACO facility due to the packaging of Atorvastatin Tablets is not expected to affect compliance with current requirements or compliance with environmental laws.

Sincerely,

Larry Seiden
Environmental and Safety Manager

Cc: M. Gallagher (PACO/West)

END

BT

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011

NDA 20702

Pg. 21 of 10/28/96
MOR

Pg. 24 of Pharm/Tox Rv

Section 5
Clinical data sources

Primary development program
This NDA includes data from 31 completed clinical pharmacology studies, 21 completed clinical studies, and 2 ongoing clinical studies.

Clinical Pharmacology Studies
All told, 590 healthy males and females received atorvastatin in clinical pharmacology studies. The demographics of this population and the exposure to atorvastatin are summarized in the tables below.

TABLE 5.1. Subject Characteristics in Clinical Pharmacology Studies

Characteristic	Placebo N = 32	Atorvastatin[a] N = 590
Sex, N (%)		
Men	21 (65.6)	341 (57.8)
Women	11 (34.4)	249 (42.2)
Race, (%)		
White	28 (87.5)	532 (90.2)
Black	4 (12.5)	39 (6.6)
Asian	0 (0.0)	2 (0.3)
Other	0 (0.0)	17 (2.9)
Age, yr		
Mean	33.9	38.9
Range	19-55	18-92

[a] Includes 24 subjects with low-density lipoprotein cholesterol (LDL-C) levels between 160 and 250 mg/dL.

13-WK ORAL TOXICITY (AMORPHOUS/CRYSTALLINE) IN RATS 10, 30, 100 mkd
CLINICAL SIGNS: "no effects" (no data)

BODY WEIGHT:
Amorphous: 11% lower HD males; decreased in M and HD females, week 1 only
Crystalline: signf. less weeks 6-12 HD males (13% lower overall);
94% gain suppression DW 7

FOOD CONSUMPTION
Amorphous: reductions DWs 3,4,7 for HD males (4-7%);
increases for M and HD females (8-12%)
Crystalline: 8% lower DW 3 (all treated)

OPHTHALMOLOGY
Amorphous: bilateral retinal hyperreflectivity (one HD male)
unilateral retinopathy with multiple hyperreflective lines (one HD female)
unilateral focal hyperreflective retina (HD female)
retinopathies (two MD females)
unilateral persistence of hyaloid vessel (LD male) incidental develop. alteration

Crystalline: unilateral retinopathy (HD male) cloudiness in central fundic area of retina
bilateral retinopathy (HD male) cloudiness in central fundic area of retina
retinal hyperreflectivity, bilateral, mild (one LD male)
retinal fold, unilateral (MD male) →"incidental develop. alteration"

HEMATOLOGY (*p<0.01):
Amorphous: no significant effects

Crystalline:	MALES
WBC:	8.46; 9.06, 10.4, 10.6*
Basophils (%):	1.13; 0.86, 0.75, 0.73*
MCHC (g/dl):	31.6; 32.5, 32.0, 332.3*

BONE MARROW	MALES	FEMALES
Amorphous:	no effects	no effects
Crystalline: (no sign. effects at p<0.01 but trend)		
Myeloid maturation index		20.6; 18.4, 20.3, 26.0