

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-740/S008/S013

ADMINISTRATIVE DOCUMENTS

Supplemental New Drug Application
Cerivastatin / BAYCOL® Patent Information

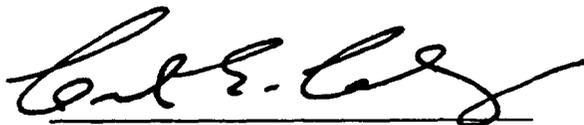
The following information is provided pursuant to 21 U.S.C. §505(c)(1) and 21 CFR §314.70(e):

US Patent Number: US Patent No. 5,006,530
Expiration Date: January 17, 2009
Type of Patent: Compound, composition and method of treating a patient
Name of Patent Owner: Bayer AG
Federal Republic of Germany

US Patent Number: US Patent No. 5,177,080
Expiration Date: January 26, 2011
Type of Patent: Compound, composition and method of treating a patient
Name of Patent Owner: Bayer AG
Federal Republic of Germany

Agent / Applicant: Bayer Corporation, residing in the United States

The undersigned declares that US Patent No. 5,006,530 and US Patent No. 5,177,080 claim the compound, compositions (formulations), and methods of treating a patient using Cerivastatin / BAYCOL®, which is the subject of this application for supplemental approval.



Carl E. Calcagni, R.Ph.
Vice President, Regulatory Affairs
Pharmaceutical Division
Bayer Corporation

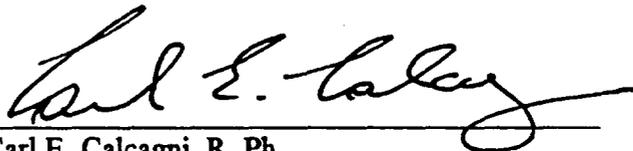
APPEARS THIS WAY
ON ORIGINAL

Section 13: The following information is hereby provided pursuant to 21 CFR 314.53(c):

Patent Number: U.S. Patent No. 5,006,530
Expiration Date: 17 January 2009
Type of patent: drug, drug product, method of use
Name of patent owner: Bayer Aktiengesellschaft
Agent: applicant (Bayer Corporation) resides in the US

Patent Number: U.S. Patent No. 5,177,080
Expiration Date: 26 November 2011
Type of patent: drug, drug product, method of use
Name of patent owner: Bayer Aktiengesellschaft
Agent: applicant (Bayer Corporation) resides in the US

The undersigned declares that Patent No. 5,006,530 and 5,177,080 each cover the composition, formulation, and/or method of use of the cerivastatin product that is the subject of this application for which approval is being sought.



Carl E. Calcagni, R. Ph.
Vice President, Regulatory Affairs
Pharmaceutical Division
Bayer Corporation

APPEARS THIS WAY
ON ORIGINAL

Section 14

All Investigations relied upon by Bayer in this NDA were conducted by or for Bayer.

APPEARS THIS WAY
ON ORIGINAL

Patent Certification

1

Exclusivity Checklist

NDA: 20-740/S-008				
Trade Name: Baycol Tablets				
Generic Name: cerivastatin sodium				
Applicant Name: Bayer Pharmaceutical Division				
Division: HFD-510				
Project Manager: William C. Koch, R.Ph.				
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	<input type="checkbox"/>	No	X
b. Is it an effectiveness supplement?	Yes	X	No	<input type="checkbox"/>
c. If yes, what type? (SE1, SE2, etc.)	SE2			
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	<input type="checkbox"/>
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.				
Explanation:				
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:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	<input type="checkbox"/>	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.				
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	<input type="checkbox"/>	No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes	<input type="checkbox"/>	No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				

APPEARS THIS WAY
ON ORIGINAL

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes		No	
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	X	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product	Baycol			
NDA #	20-740			
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	
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 <u>any one</u> 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).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. 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	X	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				

<p>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.</p>				
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	X	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.				
Basis for conclusion:				
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	X	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	X
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	X
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 #:	D97-008			
Investigation #2, Study #:				
Investigation #3, Study #:				
<p>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.</p>				
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	X
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:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				

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	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
Investigation #2	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Investigation #3	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>

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

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

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

Investigation #1	D97-008
Investigation #2	
Investigation #3	

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	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
IND#:	_____			
Explain:				
Investigation #2	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
IND#:				
Explain:				
Investigation #3	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
IND#:				
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	<input type="checkbox"/>	No	<input type="checkbox"/>
IND#:				
Explain:				
Investigation #2	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
IND#:				
Explain:				
Investigation #3	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
IND#:				
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	X
If yes, explain:				

/S/

Signature of PM

07/20/00

Date:

/S/

Signature of Division or Office Director

7/24/00

Date:

cc:
Original NDA
HFD-510/Division File
HFD-93/Mary Ann Holovac
HFD-104/TCrescenzi

APPEARS THIS WAY
ON ORIGINAL

Exclusivity Checklist

NDA:	20-740/S-013			
Trade Name:	Baycol Tablets			
Generic Name:	cerivastatin sodium			
Applicant Name:	Bayer Pharmaceutical Division			
Division:	HFD-510			
Project Manager:	William C. Koch, R.Ph.			
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	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
b. Is it an effectiveness supplement?	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
c. If yes, what type? (SE1, SE2, etc.)	SE1			
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	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
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.				
Explanation:				
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:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
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.				
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	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (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.		Yes		No	
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	X	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).					
Drug Product		Baycol			
NDA #		20-740			
Drug Product					
NDA #					
Drug Product					
NDA #					
2. Combination product.		Yes		No	
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 <u>any one</u> 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).					
Drug Product					
NDA #					
Drug Product					
NDA #					
Drug Product					
NDA #					
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. 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	X	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.					

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	X	No	
-----	---	----	--

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.

Basis for conclusion:

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	X	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	X
-----	--	----	---

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	X
-----	--	----	---

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 #:	D97-008
Investigation #2, Study #:	D91-031
Investigation #3, Study #:	D96-008

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	X
Investigation #2	Yes	X	No	
Investigation #3	Yes	X	No	

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

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	Submitted in original NDA 20-740
Investigation #3 -- NDA Number	Submitted in Supplement 00

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 X
Investigation #2	Yes	X	No
Investigation #3	Yes	X	No
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:			
Investigation #1 -- NDA Number			
Investigation #2 -- NDA Number	20-740		
Investigation #3 -- NDA Number	20-740 SEUR		
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):			
Investigation #1	D97-008		
Investigation #2			
Investigation #3			
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	Yes	X	No
IND#:	---		
Explain:			
Investigation #2	Yes	X	No
IND#:	---		
Explain:			
Investigation #3	Yes	X	No
IND#:	---		
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		No
IND#:			
Explain:			
Investigation #2	Yes		No
IND#:			
Explain:			
Investigation #3	Yes		No
IND#:			
Explain:			

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20740 **Trade Name:** BAYCOL (CERIVASTATIN)TABS
Supplement Number: 8 **Generic Name:** CERIVASTATIN
Supplement Type: SE2 **Dosage Form:** Tablet; Oral
Regulatory Action: PN **Proposed Indication:** For use as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia and mixed dyslipidemias.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Inadequate for ALL pediatric age groups
Formulation Status _____
Studies Needed STUDIES needed. Applicant has COMMITTED to doing them
Study Status Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Pediatric Written Request Letter sent February 29, 2000.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, WILLIAM C. KOCH

IS/
Signature

07/20/00
Date

5/4/00

Section 16 Debarment Certification

Bayer hereby certifies under FD&C Act, Section 306(k)(1) that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

William E. Maguire 9/22/99
William E. Maguire
Director, Clinical Quality Compliance

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-740/S008

Baycol (cerivastatin sodium tablets), 0.8mg

The Division submits the following comments:

The labeling for the preclinical sections proposed in the June 9, 2000, submission (Revised Package Insert as of June 2, 2000) is acceptable. Since the carcinogenicity studies were performed with dietary administration, this should be made clear in the carcinogenicity sections. The following terminology is recommended:

"Carcinogenesis, Mutagenesis, Impairment of Fertility: A 2-year study was conducted in rats ~~with dietary administration resulting in average daily doses...~~"

In a 2-year carcinogenicity study conducted in mice with dietary administration ~~resulting in average daily doses...~~"

If you have any questions, you may contact William C. Koch, R.Ph., Regulatory Project Manager at (301) 827-6412.

CLEARED FOR FAXING

RSI

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

6/21/00

Date

APPEARS THIS WAY
ON ORIGINAL

DETAIL REPORT

Application: NDA 20740/008 Action Goal:
 Stamp: 23-SEP-1999 District Goal: 18-JUN-2000
 Regulatory Due: 23-JUL-2000 Brand Name: BAYCOL (CERIVASTATIN) TABS
 Applicant: BAYER 50UG/100UG/300
 400 MORGAN LANE Estab. Name:
 WEST HAVEN, CT 065164175 Generic Name: CERIVASTATIN
 Priority: 1S Dosage Form: (TABLET)
 Org Code: 510 Strength: 0.2,0.3,0.4,0.8 MG

Application Comment: MANUFACTURE AND PACKAGING SITES FOR THE 0.8-MG STRENGTH ARE THE SAME THAN THOSE FOR THE APPROVED LOWER STRENGTHS. (on 19-NOV-1999 by X. YSERN (HFD-510) 301-827-6420)

FDA Contacts: X. YSERN (HFD-510) 301-827-6420, Review Chemist

Overall Recommendation:

Establishment: 1216486
 BAYER CORP
 400 MORGAN LANE
 WEST HAVEN, CT 065164175

DMF No: AADA:
 Responsibilities: FINISHED DOSAGE PACKAGER
 Profile: TCM OAI Status: NONE
 Estab. Comment: PLEASE CONFIRM CGMP STATUS OF THOSE FACILITIES. (on 19-NOV-1999 by X. YSERN (HFD-510) 301-827-6420)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-NOV-1999				YSERNX
OC RECOMMENDATION	23-NOV-1999			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: []

DMF No: AADA:
 Responsibilities: FINISHED DOSAGE MANUFACTURER
 Profile: TCM OAI Status: NONE
 Estab. Comment: PLEASE CONFIRM CGMP STATUS FOR THESE FACILITIES (RECOMMENDATION BASED ON PROFILE). (on 19-NOV-1999 by X. YSERN (HFD-510) 301-827-6420)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-NOV-1999				YSERNX
SUBMITTED TO DO	22-NOV-1999	GMP			EGASM
ASSIGNED INSPECTION	23-NOV-1999	GMP			EGASM
INSPECTION SCHEDULED	09-APR-2000		20-APR-2000		IRIVERA
INSPECTION PERFORMED	09-MAY-2000		20-APR-2000		EGASM

> Form 483 issued

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 20740/008
Stamp: 23-SEP-1999 Regulatory Due: 23-JUL-2000
Applicant: BAYER
400 MORGAN LANE
WEST HAVEN, CT 065164175

Priority: 1S
Action Goal:
Brand Name: BAYCOL (CERIVASTATIN) TABS
50UG/100UG/300
Established Name:
Generic Name: CERIVASTATIN
Dosage Form: TAB (TABLET)
Strength: 0.2,0.3,0.4,0.8 MG

Org Code: 510

District Goal: 18-JUN-2000

FDA Contacts: X. YSERN (HFD-510) 301-827-6420 , Review Chemist

Overall Recommendation:

Establishment: 1216486
BAYER CORP
400 MORGAN LANE
WEST HAVEN, CT 065164175

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-NOV-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment: [

] DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: INSPECTION PERFORMED
Milestone Date: 09-MAY-2000

Responsibilities: FINISHED DOSAGE
MANUFACTURER

*inspection performed 17-APR-00 completed 20-APR-00
by investigator Debra Bennett
CMP classification VAI
Form 4836 issued YCV*

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Attached	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME William E. Maguire		TITLE Director, Clinical Quality Compliance	
FIRM/ORGANIZATION Bayer Corporation, Pharmaceutical Division			
SIGNATURE <i>William E. Maguire</i>		DATE September 22, 1999	

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

WITHHOLD 2 PAGES

NDA 20-740/S-008

Baycol (cerivastatin sodium tablets)

Bayer Corporation

Drug class: lipid altering, HMG-CoA reductase inhibitor

Date of submission: September 22, 1999

Note to the file

The safety update review for this sNDA is contained in the medical officer review.

David G. Orloff, M.D.
Medical Tm Ldr
DMEDP/CDER/FDA

1S/
7-17-00

APPEARS THIS WAY
ON ORIGINAL

NDA 20-740/S-008, S-013

Baycol (cerivastatin sodium tablets)

Bayer Corporation

Drug class: lipid altering, HMG-CoA reductase inhibitor

Date of submission: September 22, 1999

Date of review: July 19, 2000

Proposed:

S-008: To market a dosage strength of 0.8 mg and extend the dosing range to 0.8 mg daily

S-013 : To add to Indications and Usage the phrase "and to increase HDL-C" reflecting the expectation of this potential benefit of treatment with cerivastatin in patients with Type IIa and IIb hyperlipoproteinemia

Team leader note on supplemental NDA

Materials reviewed

This review is written based upon the medical officer review dated 7-6-00 and on review of the sponsor's Overall Summary contained in volume 1.1 of the original submission.

Purpose of S-008

This sNDA proposes marketing of a higher dosage strength of cerivastatin, 0.8 mg, which constitutes a doubling from the previous highest dose of 0.4 mg. The initial approval of cerivastatin in 6/97 was for 0.2 and 0.3 mg, and the approval of the 0.4 mg dose followed in 5/99. The current labeling cites mean LDL-C reductions of 25%, 31%, and 34%, respectively for the three approved doses, in order of increasing strength.

Clinical trials conducted in support of safety and efficacy of cerivastatin 0.8 mg

The current application relies on the data from two trials that investigated the safety and efficacy of the 0.8 mg dose. The first trial (D97-008) was a large, randomized, double-blind, multicenter, placebo/active controlled trial of 52 weeks' duration conducted in the U.S. and Canada, comparing ceriva 0.8 and 0.4 to placebo/pravastatin 40 mg.

Randomization to three treatment groups, as above, was in a ratio of 4:1:1, with approximately 800 patients randomized to cerivastatin 0.8 mg. The second study (International study 17) was a multicenter, randomized, double-blind forced titration study comparing the safety and efficacy of cerivastatin up to 0.8 mg with simvastatin up to 40 mg. There were 185 and 184 patients randomized to cerivastatin and simvastatin, respectively. The results of this study were submitted as part of the 4-month safety update. Dr. Shen's review contains details of the protocols from these two studies. This review will focus on the essential data in support of safety and efficacy, largely derived from the larger trial, Study -008.

Efficacy (S-008, S-013)

For analyses of efficacy, the sponsor utilized two pools of clinical trial data. On the one hand, for principal analyses, a pool including study -008 and 3 other lower-dose cerivastatin placebo-controlled studies, all with an 8-week timepoint in common, was utilized (Pool 1). For analyses of effects on TG and HDL, for which a larger sample size

was needed, the sponsor pooled study -008 with 7 other lower dose cerivastatin controlled trials.

The efficacy of cerivastatin 0.8 mg is established by the results of study -008 and the lipid response analyses from Pool 1 form the basis for table 1 in the proposed revised label, reproduced as Table 1, below. In addition, the results of study -008 show that, as for other statins and consistent with what has been demonstrated previously for cerivastatin at lower doses, the effect of the 0.8 mg doses on LDL-lowering is seen by 2 weeks and the peak mean effect is seen at 4 weeks (results not shown).

In addition, the LDL-C lowering data are consistent with the well-characterized effects of drugs in this class insofar as with each successive doubling of cerivastatin dose, there is an incremental 8-9% further reduction in LDL-C from baseline. The general finding across the class is cited as "the rule of 5" for TC lowering and the "rule of 7" for LDL-C lowering, denoting the incremental lowering from baseline with successive doublings of statin dose.

Table 1. Mean % change from baseline to week 8. Pool 1 (ITT).

	N	Total-C	LDL-C	Apo B	TG	HDL-C	LDL-C/HDL-C	Total-C/HDL-C
Placebo	608-620	+1	0	+1	0	+2	-1	0
Baycol								
0.2 mg	150-151	-18	-25	-19	-16	+9	-31	-24
0.3 mg	494-497	-22	-31	-24	-16	+8	-35	-27
0.4 mg	754-758	-24	-34	-27	-16	+7	-38	-29
0.8 mg	731-735	-30	-42	-33	-22	+9	-46	-35

Other labeling changes related to S-008

The sponsor also proposes amending tables 2 and 3 in the current label to include data from study -008. Table 2 of the label summarizes the TG and HDL-C response data from the subset of Pool 2 with baseline TG between 250 and 500 mg/dL and demonstrates, as shown across the class, that the magnitude of TG lowering and HDL-C raising are directly related to baseline TG. Table 3 of the label summarizes the lipid response data from study -008 with regard to percent of patients reaching NCEP goals for LDL-C as a function of risk group.

Analyses specifically supporting S-013

The changes from baseline in HDL-C and TG levels, summarized in Table 1, across the cerivastatin dosage range, were statistically significantly different from placebo. Consistent with the recent changes to the labeling for simvastatin, atorvastatin, and pravastatin, the sponsor proposes to convey in labeling the expected effect of cerivastatin on HDL-C in patients with Type IIa and IIb hyperlipoproteinemia. This is accomplished by the additional inclusion in Clinical Pharmacology of the distribution of HDL effects across the dosage range (median, 25th, 75th percentiles) and with the addition of language to Indications reflecting the expectation of an increase in HDL-C in response to cerivastatin. The label already contains a disclaimer, also shared across the class, to the effect that while elevated TG and HDL-C are predictors of increased and decreased CHD

risk, respectively, the independent effects of lowering TG or of raising HDL-C on the risk for CHD have not been established. Minor changes were recommended to this disclaimer and accepted by the sponsor.

Conclusions regarding efficacy in support of S-008 and S-013

The incremental lowering of LDL-C seen with cerivastatin 0.8 mg relative to 0.4 mg is consistent with the rest of the statin class and as expected based upon the previous experience with cerivastatin. Similarly, the effects on the other lipid and apoprotein parameters summarized in the table reproduced above are consistent with a doubling of the 0.4 mg dose.

The data on the efficacy of cerivastatin across the dosage range to raise HDL-C in patients with Fredrickson Types IIa and IIb hyperlipoproteinemia are consistent with the rest of the statin class. There is no dose response seen, also consistent with the class. The responses across individual patients are variable, though in a substantial fraction of patients studied, the changes in HDL-C are potentially clinically significant and merit inclusion in the label in order to convey this expected response to cerivastatin.

Safety (S-008)

The safety exposure for cerivastatin 0.4 and 0.8 mg in study -008 is summarized in table 2, below.

Number of patients treated with cerivastatin by dose and duration in Study -008

Dose	8 weeks	24 weeks	52 weeks
Ceriva 0.4	185	175	126
Ceriva 0.8	728	686	491

Across the statin class, two principal safety concerns have been the focus of evaluation in clinical trials and the focus of monitoring in clinical use. These are elevations in hepatic transaminases and myopathy. While the incidence of any elevation in transaminase as well as of elevations to ≥ 3 X ULN (defined as clinically significant) appears to increase with increasing dose for statins in general, there is very little evidence to suggest that statins, cerivastatin included, cause serious liver disease. In our recent examination of the post-marketing data for lovastatin and pravastatin (June 2000), the reporting rate for hepatic failure in association with the use of either drug did not exceed background. Furthermore, it is worth noting that from the megatrials with pravastatin and simvastatin, the pattern also emerges that among patients with normal transaminases at baseline or after several months of therapy (i.e., no underlying liver disease and/or risk factors for elevations in transaminases), the incidence of repeated elevations in transaminases is extremely low. The LFT data from the clinical trials of cerivastatin will be reviewed briefly below. Suffice it to say that the incidence of repeat (not necessarily consecutive) elevations in either SGOT or SGPT to ≥ 3 X ULN is $< 1\%$ across the dosage range of cerivastatin through 1 year of treatment.

Much more serious than mild, asymptomatic, benign elevations in transaminases associated with statin use is another side effect, also presumably related to the mechanism of action of the drug, myopathy. While the precise mechanism is not known, this also

appears to be dose-related, or at least systemic-plasma-level related. In rare but remarkable and unfortunate instances, statins have been associated with full-blown rhabdomyolysis, complicated by acute renal failure. These cases have often involved concomitant use of drugs either with a known capacity to induce rhabdomyolysis themselves or that are known to interact with the culprit statin to affect the pharmacokinetics of the HMG-CoA reductase inhibitor, increase systemic exposure, and presumably thereby precipitate myopathy. While this is a rare event, as implied above, it is potentially catastrophic, and patients are told to stop the drug if they develop flu-like symptoms of diffuse muscle aches and pains and/or weakness, and to see a physician.

Elevations in SGOT or SGPT

Dr. Shen has reviewed the summary information on elevations in hepatic transaminases from studies -008 and 17. With specific regard to clinically significant elevations (SGOT or SGPT > 3X ULN on 2 or more (not necessarily consecutive) occasions, regardless of baseline status, the results from the pool of cerivastatin U.S. studies added to study -008 are summarized in table 3, below. The mean treatment duration in this pool was 11 months.

Table 3. Number of cerivastatin-treated patients with SGOT or SGPT $\geq 3 \times$ ULN on 2 or more occasions (not necessarily consecutive) regardless of baseline LFT status, by dose of drug.

Ceriva dose (N)	0.05 mg (192)	0.2 mg (771)	0.3 mg (914)	0.4 mg (900)	0.8 mg (774)	Total* (3776)
Number of cases (%)	1 (0.5)	1 (0.1)	4 (0.4)	8 (0.9)	4 (0.5)	18 (0.5)

*The total includes patients treated with other doses of cerivastatin, at which no cases occurred.

The information in the table is included in proposed labeling, and recommendations regarding LFT monitoring are likewise included in WARNINGS. No changes are proposed by the sponsor or suggested by the Division.

Myopathy and elevations in CK

In study -008, through 52 weeks of follow up, the overall incidences of CK elevations above the upper limit of normal (ULN) were 35%, 38%, and 49% for the placebo/prava 40 mg, ceriva 0.4, and ceriva 0.8 mg groups, respectively. Of clinical relevance, the incidences of elevations $\geq 10X$ ULN with or without symptoms across the treatment groups, as above, were 1%, 2%, and 2%, respectively. The majority (>75%) of these events occurred within the first 2 months of treatment, implying a predetermined individual susceptibility not related to cumulative exposure. There were no cases of rhabdomyolysis in this study or in the ceriva 0.8 mg development program as a whole.

The most remarkable finding with regard to this potential adverse effect of cerivastatin is discussed in Dr. Shen's review and in the sponsor's summary. This relates to the observation in study -008 of an increased incidence of CK elevations in the older women treated with cerivastatin in the trial.

To summarize, there were 15 patients treated with cerivastatin 0.8 mg in this study who developed at least tenfold CK elevations. Of these, 8 were women and 7 were men. All 8 women were > 63 years of age while the men were aged 24-57 years. The women also had lower body weights than the males, ranging from 59-74 kg, while the men's weights ranged from 84-106 kg. Of note, and consistent with a greater exposure in the 8 affected women, the mean reduction in LDL-C across this group was 53%, while that in the women without tenfold CK elevations was 45%. Men overall showed less of an effect of cerivastatin 0.8 mg, with an overall mean LDL-C lowering of approximately 40% and, surprisingly, a lower than average mean LDL-C reduction among the men with tenfold CK elevations.

Overall, in Study -008, the incidence of tenfold CK elevations among males of all ages treated with cerivastatin 0.8 mg was 1-2% through week 52 of the follow up. Among the women \geq 65 years of age treated with cerivastatin 0.8 mg, the incidence was 6-7%. Similarly, for the small group of women \geq 65 years of age treated with cerivastatin 0.4 mg in Study -008 (N=27), the incidence of tenfold CK elevations through week 52 was 7-8% (2 cases).

The incidence of tenfold CK elevations across the dosage range of cerivastatin remains rare (<1%), though the finding from study -008 of an increased risk among older women merits concern and treatment in labeling.

Conclusions on the safety of cerivastatin 0.8 mg

The only concern arising out of the development program relates to the increased risk for myopathy among older women suggested by the observation in Study -008. Indeed, this increased risk may well apply to lower doses of cerivastatin as well. It appears related to increased exposure, as suggested by the augmented LDL-lowering efficacy observed among the small group of older women with tenfold CK elevations in this trial. At the request of the Division, the apparent increased risk is noted in the WARNINGS section of the label and caution when titrating to the 0.8 mg dose is recommended in PRECAUTIONS, Geriatric Use. Of note, labeling for all the statins contains bolded statements in WARNINGS about the risk of myopathy and rhabdomyolysis as well as recommendations to discontinue the drugs if myopathy is diagnosed or suspected based on laboratory studies and/or symptoms.

Financial disclosure

Financial disclosure information was received from all investigators.

NDA 20-740/S-008, S-013
Baycol 0.8 mg dosage strength
Add HDL increase to indications

With regard to issues of the investigators' financial arrangements and disclosure, the integrity of the clinical trial data submitted is not in question.

DSI inspections

The Division of Scientific Investigations inspected 3 clinical sites for Study D97-008. There were two 483 forms issued related to minor protocol deviations that have no bearing on overall data integrity.

Overall Summary and Conclusions

The safety and efficacy of cerivastatin 0.8 mg have been adequately addressed in the large Phase 3 trial conducted in support of this sNDA. In addition, a smaller forced-titration study in which about 185 patients were treated with cerivastatin up to 0.8 mg daily for 12 weeks, reviewed in detail by Dr. Shen, contributed to the safety database for this sNDA.

Taking into account the risk of rare adverse events associated with cerivastatin 0.8 mg and the benefit of the additional LDL-lowering efficacy that it affords, this dosage strength should be approved.

The data summarizing the efficacy of cerivastatin in raising HDL-C levels in patients with primary elevations in LDL-cholesterol with or without elevated TG support approval of the proposed changes to the Clinical Pharmacology and Indications and Usage sections of the label (S-013).

Recommendation

Pending final agreement on labeling, these supplemental NDAs should be approved.

David G. Orloff, M.D.
Deputy Director/Med. Tm. Ldr.
DMEDP/CDER/FDA

/S/

7-19-00

Recommendation code: AP

CC:
NDA 20-740 Arch
HFD-510

*Conan,
Application should
be approved.
/S/*

TT 7/21/00

BEST POSSIBLE COPY

MAR 14 2001

William Insull, Jr., M.D.
Director, Lipid Research Clinic
Baylor College of Medicine
The Methodist Hospital
6565 Fannin, B120
Houston, TX 77030

Dear Dr. Insull:

Between February 1 and February 7, 2000, Mr. Patrick Stone, representing the Food and Drug Administration (FDA), inspected your conduct as the investigator of record of a clinical study (Protocol #D97-008-09) of Baycol (cerivastatin) that you conducted for Bayer Corporation. From our evaluation of the inspection report prepared by Mr. Stone, we conclude that you conducted your study in compliance with applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Investigator Stone during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL



MAR 31 2000

Evan Stein, M.D.
2350 Auburn Avenue
Cincinnati, OH 45219

Dear Dr. Stein:

Between January 31 and February 8, 2000, Ms. Gina Brackett, representing the Food and Drug Administration (Agency), inspected your conduct as the investigator of record of your clinical study (Protocol D97-008) of the investigational drug cerivastatin. You conducted your study for Bayer Corporation. This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, Ms. Brackett presented her inspectional observations (i.e., Form FDA 483) and discussed these observations with you. From our evaluation of the inspection report and your oral responses to the inspectional observations, we conclude that you did not adhere to the Federal regulations and good clinical practices governing your conduct of clinical studies of investigational new drugs and the protection of human subjects. In particular, we note that you failed to conduct your study in accordance with the approved protocol in that certain subjects met the exclusion criteria of the protocol yet were included or continued in the study without sponsor notification and approval.

Specifically, you failed to follow the protocol in that subject #27035 was not on a stable dose of thyroid hormone replacement prior to entry into the study at Visit 1 as required by the protocol. Subject # 27030 had a fasting blood glucose level of 145 mg/dl at Visit 1 and was included in the study though the protocol provided for exclusion of subjects whose blood glucose levels exceeded 140 mg/dl. Subject #27024 was taking a corticosteroid prohibited by the protocol but was not excluded from the study. Subject #27022 was taking an H2 blocker which was prohibited by the protocol but was not excluded from the study. Also, subjects #27039 and # 27026 took less than 80% of the prescribed regimen on two consecutive visits but were not excluded from the study as required by the protocol.

Please ensure that corrective actions will be taken to prevent similar problems in your current and future studies.

We appreciate the cooperation shown Ms. Brackett during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

/S/

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

**APPEARS THIS WAY
ON ORIGINAL**